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REVIEW ARTICLE

Comparing milled fiber, Quebec ore, and textile factory dust: Has another piece of the asbestos puzzle fallen into place?

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Abstract

Results of a meta-analysis indicate that the variation in potency factors observed across published epidemiology studies can be substantially reconciled (especially for mesothelioma) by considering the effects of fiber size and mineral type, but that better characterization of historical exposures is needed before improved exposure metrics potentially capable of fully reconciling the disparate potency factors can be evaluated. Therefore, an approach for better characterizing historical exposures, the Modified Elutriator Method (MEM), was evaluated to determine the degree that dusts elutriated using this method adequately mimic dusts generated by processing in a factory. To evaluate this approach, elutriated dusts from Grade 3 milled fiber (the predominant feedstock used at a South Carolina [SC] textile factory) were compared to factory dust collected at the same facility. Elutriated dusts from chrysotile ore were also compared to dusts collected in Quebec mines and mills. Results indicate that despite the substantial variation within each sample set, elutriated dusts from Grade 3 fiber compare favorably to textile dusts and elutriated ore dusts compare to dusts from mines and mills. Given this performance, the MEM was also applied to address the disparity in lung cancer mortality per unit of exposure observed, respectively, among chrysotile miners/millers in Quebec and SC textile workers. Thus, dusts generated by elutriation of stockpiled chrysotile ore (representing mine exposures) and Grade 3 milled fiber (representing textile exposures) were compared. Results indicate that dusts from each sample differ from one another. Despite such variation, however, the dusts are distinct and fibers in Grade 3 dusts are significantly longer than fibers in ore dusts. Moreover, phase-contrast microscopy (PCM) structures in Grade 3 dusts are 100% asbestos and counts of PCM-sized structures are identical, whether viewed by PCM or transmission electron microscope (TEM). In contrast, a third of PCM structures in ore dusts are not asbestos and only a third that are counted by PCM are also counted by TEM. These distinctions also mirror the characteristics of the bulk materials themselves. Perhaps most important, when the differences in size distributions and PCM/TEM distinctions in these dusts are combined, the combined difference is sufficient to completely explain the difference in exposure/response observed between the textile worker and miner/miller cohorts. Importantly, however, evidence that such an explanation is valid can only be derived from a meta-analysis (risk assessment) covering a diverse range of epidemiology study environments, which is beyond the scope of the current study. The above findings suggest that elutriator-generated dusts mimic factory dusts with sufficient reliability to support comparisons between historical exposures experienced by the various cohorts studied by epidemiologists. A simulation was also conducted to evaluate the relative degree that the characteristics of dust are driven by the properties of the bulk material processed versus the nature of the mechanical forces applied. That results indicate it is the properties of bulk materials reinforces the theoretical basis justifying use of the elutriator to reconstruct historical exposures. Thus, the elutriator may be a valuable tool for reconstructing historical exposures suitable for supporting continued refinements of the risk models being developed to predict asbestos-related cancer risk.

Keywords: *Asbestos; chrysotile; elutriator; fiber size; lung cancer; mining; PCM; PCME; TEM; textile*

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Introduction

The potential for asbestos to cause lung cancer and mesothelioma is well established (as reviewed in IRIS Current; Nicholson, 1986; OSHA, 1992; ERG, 2003; Berman and Crump, 2008a, 2008b). However, the potency (exposure/response) factors estimated for these diseases vary substantially across the epidemiology studies from which they were derived (Nicholson, 1986; Berman and Crump, 2008a). The recent meta-analysis by Berman and Crump (2008b) indicates that the variation in potency factors can be substantially reconciled (especially for mesothelioma) by considering the effects of fiber size and mineral type, but that better characterization of the relevant, historical exposures is needed before improved exposure metrics[1] that are potentially capable of fully reconciling the disparate potency factors can be evaluated.

Among other things, the above highlights the question of how data useful for better characterizing historical exposures might be developed. The relative merits of traditional approaches for better characterizing historical exposures are evaluated in the Background section of this study, and although each can be applied to some exposure environments of interest, numerous environments exist in which none are applicable (primarily due either to a lack of samples or limits to the utility of the existing data). Therefore, a candidate approach is also identified that can potentially be applied to some of the environments for which traditional approaches are not helpful.

The Modified Elutriator Method (Berman and Kolk, 1997, 2000) can be used to generate dusts from appropriately selected bulk materials that potentially reproduce the characteristics of dusts generated by commercial mining, milling, handling, or other processing of similar materials and the theory supporting use of the Modified Elutriator Method for this purpose is presented in the Background section. However, neither the degree with which, nor the circumstances under which, the characteristics of dusts generated by elutriation adequately reproduce those of dusts generated historically (during commercial processing) have been adequately explored. Consequently, the first objective of this study is to evaluate the performance of this new approach.

To address this first objective, dusts generated by elutriation of Grade 3 milled fiber are compared to dusts on archived air-sample filters collected at the South Carolina textile facility studied by Dement et al. (2007). As indicated in the background discussion, Grade 3 fiber is the type of material most commonly used in the manufacture of asbestos textiles in South Carolina and access to the raw

[1]An exposure metric is a weighted set of size categories that are defined in the counting rules of an analytical method used to determine asbestos concentrations. The phase-contrast microscopy (PCM) metric, for example, is the set of all structures longer than 5 μm (micrometers) with an aspect (length to width) ratio greater than 3 when viewed using PCM as described in NIOSH Method 7400 (NIOSH, 1994a).

(unsummarized) data from the Dement et al. study facilitated detailed comparison of these data sets. Elutriator-generated dusts from Quebec ore are also compared to published characterizations of dusts from chrysotile mines and mills. However, this comparison is necessarily less rigorous, as access was limited to the summarized data from a published study (Gibbs and Hwang, 1980). Similarly, the elutriated dusts from Grade 3 were also compared to published characterizations of textile factory dusts published in an earlier study (Dement and Harris, 1979).

Once the performance of the Modified Elutriator Method was established, the approach was applied to address an outstanding issue also identified by Berman and Crump (2008b). The single largest discrepancy that remains to be reconciled among the epidemiology studies evaluated by Berman and Crump is the difference between the lung cancer potency factors estimated respectively for South Carolina textile workers (most recent follow-up: Hein et al., 2007) and chrysotile miners/millers in Quebec (most recent follow-up: Liddell et al., 1997). These are both high-quality studies so that confidence intervals are narrow and the difference between their lung cancer potency factors is significant.

Given the above, the second objective of this study is to evaluate whether improved consideration of the effects of fiber size and mineral type can potentially reconcile the lung cancer potency factors from the South Carolina textile and Quebec mine studies. To accomplish this, elutriated dusts from Grade 3 material (used to represent exposures in the South Carolina textile factory) and from raw chrysotile ore (used to represent dusts to which Quebec miners and millers were exposed) are compared. In such comparisons, exposure metrics were explored that can potentially reconcile the difference in potency factors observed between these two cohorts.

Importantly, potency factors reported by Berman and Crump (2008a) are used in this study to develop a numerical target against which the potential performance of candidate exposure metrics can be evaluated. However, the current study is not a formal assessment of asbestos-associated cancer risk because it does not compare potency estimates across a broad range of environments, as is done in existing meta-analyses (e.g., Nicholson, 1986; Berman and Crump, 2008b). Therefore, exposure metrics identified in this study, which potentially reconcile the disparate potency estimates respectively observed among South Carolina textile workers and Quebec miners/millers, should only be considered suggestive; suggested metrics will require further validation that demonstrates their ability to fully reconcile the disparate potency factors observed across a broad range of epidemiology studies. This, in turn, will require a future meta-analysis to be conducted once historical data are better characterized from a sufficiently broad range of epidemiology studies to support a full and robust evaluation. Also because this is not a formal risk assessment, detailed consideration of other factors (e.g., smoking) that potentially affect asbestos-related cancer risk are beyond the intended scope.

The current study is part of ongoing work aimed at (1) better quantifying asbestos-related risk and (2) better defining the characteristics of the fibers that contribute to such risk.

Background

The effects of structure[2] size and mineral type on asbestos cancer potency

Berman and Crump (2008a) provide estimates of the potency of asbestos for causing lung cancer or mesothelioma that were developed from published studies (including unsummarized data from three of the studies) of occupationally exposed cohorts covering a diverse range of exposure environments. Results of this analysis are expressed as study-specific potency factors for lung cancer (denoted by K_L) and mesothelioma (denoted by K_M), along with "uncertainty bounds" for these factors that account for both statistical and nonstatistical uncertainty, including uncertainty in exposure to asbestos (Berman and Crump, 2008a, Tables 3 and 4).

As was also the case in an earlier study (Nicholson, 1986), which supported development of the unit risk factor for asbestos in current use by the US Environmental Protection Agency (EPA) (IRIS Current), Berman and Crump (2008a) found substantial variability among the K_L's and K_M's estimated from different environments. Among the 20 studies evaluated (from 18 unique environments), K_L's vary by almost 2 orders of magnitude (ignoring one negative study that would otherwise make the range infinite) and K_M's by more than 3 orders of magnitude. Moreover, differences across several of the studies were shown to be statistically significant.

The same risk models were used both by Berman and Crump (2008a) and Nicholson (1986) to estimate K_L's and K_M's by fitting the risk models to the available exposure and mortality data from each epidemiology study. These models incorporate two critical assumptions: (1) that there is no difference in the potencies of different mineralogical types of asbestos (i.e., chrysotile or different varieties of amphibole asbestos) in causing lung cancer or mesothelioma; and (2) that risk can be predicted from exposures quantified using phase-contrast microscopy (PCM), which provides counts only structures of longer than 5 μm, thicker than approximately 0.25 μm,[3] and with an aspect (length-to-width) ratio greater than three (NIOSH, 1994a, 1994b).

Increasing evidence indicates that neither of the above assumptions is valid and that differences in structure size

[2]As used here and throughout, the term "structure" is intended to include not only single fibers (fibrils), but the bundles, clusters, and matrices that make up the set of fibrous particles in an asbestos dust (ISO, 1995).

[3]Due to the limitations of optical microscopy, when analyzed using other analytical techniques (such as transmission electron microscopy [TEM]), the metric is limited to structures thicker than 0.25 μm (NIOSH, 1994a, 1994b). By limiting widths in this manner, structures respectively included when PCM-sized structures are determined by TEM (the PCM-equivalent or PCME metric) and the PCM metric (determined by PCM) are better matched.

and type may account for the disparate estimates of potency obtained in different environments. For example, as initially suggested by animal implantation studies conducted by Stanton and coworkers (1972, 1977, 1981) and confirmed by many others (Bertrand and Pezerat, 1980; Bonneau et al., 1986a, 1986b; Bolton et al., 1982, 1983, 1986; Davis et al., 1985, 1986a, 1986b, 1987, 1988; Muhle et al., 1987; Pott et al., 1972, 1974, 1976, 1982, 1987; Wagner et al., 1976, 1982, 1985; Wylie et al., 1987, 1993; Goodglick and Kane, 1990; reviewed in Berman and Crump, 2003), carcinogenicity is mediated by a structure's size. These studies suggest, for example, that potency increases with increasing length and thinner structures may contribute more to potency than thicker structures.

A meta-analysis of animal inhalation studies (Berman et al., 1995; updated in Berman and Crump, 2003) indicates that potency toward both lung cancer and mesothelioma is best predicted by structures thinner than 0.4 μm that are at least 5 μm in length, with those longer than 40 μm being more than 400 times as potent as those between 5 and 40 μm. These authors also found, in contrast, that the tumor incidence data could not be fit with exposures estimated as concentrations of PCM structures (the metric by which exposure concentrations are most commonly reported in epidemiology studies). Others have also proposed that specific dimensional categories (differing from those traditionally counted by PCM) may best correlate with induction of the various asbestos related diseases in humans (Lippmann, 1988, 1994, 1999; Stayner et al., 2007; Berman and Crump, 2003). Results of their more recent meta-analysis (Berman and Crump, 2008b) also confirms that structures substantially longer than those traditionally counted by PCM best predict both lung cancer and mesothelioma risks in humans, although limitations in the available data precluded testing of hypotheses involving structure size categories with minimum lengths greater than 10 μm. Yet, some of the studies cited above suggest a need to separately consider structures longer than 40 μm to adequately assess risk.

Regarding structure type, mesothelioma rates among cohorts exposed primarily to amphibole asbestos are substantially higher than rates observed among those exposed primarily to chrysotile and it is generally agreed that amphibole asbestos is more potent in inducing mesothelioma in humans than chrysotile (Mossman et al., 1990; Hodgson and Darnton, 2000; ERG, 2003; Berman and Crump, 2003, 2008a, 2008b).

Due to the observation that chrysotile deposits from some environments are associated with small amounts of amphibole, usually tremolite (William-Jones et al., 2001), and because lung tissue samples from cohort members thought to have been exposed predominantly to chrysotile have exhibited tremolite and even commercial amphibole asbestos in their lungs (Case, 1991; Case and Sebastien, 1987, 1989; Case et al., 1997, 2000; McDonald et al., 1997), it has been hypothesized that chrysotile does not cause mesothelioma and that the mesothelioma observed among cohorts exposed primarily to chrysotile is in fact due entirely to the presence of contaminating amphibole (or other durable asbestiform[4] minerals such as balangeroite; Piolatto et al., 1990). This "amphibole hypothesis" has been debated in the literature for more than 20 years (McDonald and Fry, 1982; Churg et al., 1984; Huncharek, 1987; McCoinnochie et al., 1987; Dunnigan, 1988; Becklake, 1988; Mancuso, 1988; McDonald, 1988; Churg, 1988a, 1988b; Sluis-Cremer 1988; Langer and Nolan, 1989; Ohlson, 1989; McDonald et al., 1989; Sebastien et al., 1989; Rogers et al., 1991; Tuomi, 1992; Roggli et al., 1993; Mossman, 1993; Elmes, 1994; Ross and McDonald, 1995; Berman et al., 1995; Smith and Wright, 1996; Smith, 1998; Dumortier et al., 1998; Schneider et al., 1998; Miller et al., 1999; Pooley and Wagner, 1988) and remains to be definitively resolved. However, based on the sensitivity analysis included in the recent study by Berman and Crump (2008b), the minimum difference in mesothelioma potency between chrysotile and amphibole asbestos is at least 2 orders of magnitude and the possibility that chrysotile is nonpotent toward mesothelioma induction could not be ruled out.

In contrast, while evidence is clear that amphibole asbestos is more potent than chrysotile *toward the induction of* mesothelioma, whether there is a difference in potency toward lung cancer remains controversial. Although there are suggestions of a difference, recent meta-analyses show mixed results (Stayner et al., 1996; Lash et al., 1997; Hodgson and Darnton, 2000; Berman and Crump, 2003, 2008b). An important implication of these observations is that although structure type plays a major role in mediating potency toward mesothelioma, structure size may dominate lung cancer potency.

The meta-analysis by Berman and Crump (2008b) indicates that by addressing structure size and type, the degree of agreement in K_L's and especially K_M's is substantially improved over that provided by traditional use of PCM-sized structures, although differences across the published studies are not entirely reconciled. As a result, despite these studies and inferences from the broader literature (see Berman and Crump, 2003), the quantitative effects of structure type and size remain somewhat controversial (e.g., Walton, 1982; ERG, 2003; Berman and Crump, 2008a, 2008b).

As indicated in Figure 2 of Berman and Crump (2008b), among the cohorts evaluated, it is only the lung cancer potencies estimated from the cohort of South Carolina Textile Workers (Hein et al., 2007) and the cohort of chrysotile miners/millers (Liddell et al., 1997) that remain to be adequately fit by the exposure metrics evaluated in that study, and because the difference in potencies estimated for these cohorts is also among the largest, the difference in potencies between these two cohorts remains the most important difference that needs to be reconciled, if the lung

[4]The term "asbestiform" means the particular crystalline form (habit) of a mineral that exhibits the properties of asbestos (composed of high-tensile-strength fibers that are flexibility and resistant to chemical and thermal attack).

cancer potency of asbestos is to be adequately modeled so that it can be predicted.
In summary,

- the exposure metrics evaluated by Berman and Crump (2008b) incorporate consideration of structure size and type, but (for size) only to the extent that existing data allowed;
- better characterization of historical exposures will be required before it will be possible to test hypotheses incorporating separate categories for the longer and thinner structures that animal studies suggest will be required to fully reconcile the existing epidemiology;
- excluding consideration of structure size and type, the K_L's obtained from South Carolina textile workers and Quebec miners/millers, which represent the predominant unresolved discrepancy for lung cancer, vary by a factor of 47, and, more importantly, their uncertainty intervals do not overlap (Berman and Crump, 2008a, Table 3); and
- as evidence for an effect of mineral type on lung cancer is equivocal (and small in any case), reconciling disparate potency estimates for lung cancer will potentially be driven by structure size.

The disparity in lung cancer potency observed among textile workers and chrysotile miners/millers

The discrepancy in lung cancer potency between Quebec miners/millers (Nicholson et al., 1979; McDonald et al., 1980, 1993; most recent follow-up: Liddell et al., 1997) and Charleston, South Carolina, textile workers (Dement, 1980; Dement and Brown, 1998; Dement et al., 1982, 1983a, 1983b; McDonald et al., 1983a; most recent follow-up: Hein et al., 2007), who mainly processed chrysotile from Quebec and similar mines, has been recognized and evaluated by numerous researchers (Berman and Crump, 2003, Appendix D; Case et al., 2000; Dement and Brown, 1994; McDonald, 1998; Sebastien et al., 1989; Stayner et al., 2007). Moreover, the reasonably good agreement in lung cancer potency estimates observed between Quebec chrysotile miners/millers and Italian chrysotile miners/millers (Piolatto et al., 1990) and between South Carolina textile workers and workers from both a Pennsylvania textile factory (McDonald et al., 1983b) and a factory in Rochdale, England (Peto, 1980a, 1980b; Peto et al., 1985) suggest that the differences between Quebec and South Carolina may reflect a general difference between these two industries (Berman and Crump, 2003, 2008a).

Three main hypotheses have been advanced to explain the difference in the risk per unit exposure observed among miners and textile workers (see, for example, Sebastien et al., 1989). These are

1. the low reliability of exposure estimates in the various studies;
2. differences in structure size distributions in the two industries (with textile-related exposures presumably involving greater fractions of longer structures); or
3. simultaneous exposure to a co-carcinogen (i.e., oil that may have been sprayed on asbestos fibers) in the textile industry.

It has also been proposed that differences in the concentration of long tremolite (amphibole) structures in dusts from each of the two industries might represent an explanatory factor (see, for example, McDonald, 1998b). This hypothesis might also be expanded to include amphiboles in general, as lung tissue studies suggest that South Carolina textile workers may have been exposed to commercial amphibole asbestos in addition to chrysotile (Case et al., 2000; Green et al., 1997). However, this would also require a large relative difference between the potencies of tremolite (amphiboles) and chrysotile toward the induction of lung cancer, as the vast majority of the structures to which both of these cohorts were exposed was chrysotile. As indicated in the previous section, whether amphibole asbestos is more potent than chrysotile toward the induction of lung cancer is currently unclear. Coupled with the observation that mesothelioma potencies observed in the South Carolina textile and Quebec mining cohorts are similar (Berman and Crump, 2008a), it is unlikely that differences in (the minor) amphibole exposures between these two cohorts can explain the observed difference in lung cancer potency. Therefore, this is more likely to be an effect of structure size than structure type.

The first of the above-listed hypotheses was evaluated by Sebastien et al. (1989). These authors compared lung fiber concentrations determined in tissue samples from deceased members of both the South Carolina and Quebec cohorts to the corresponding levels and durations of exposure experienced by these cohort members. Sebastien et al. found that despite large variation in the relationship between fiber concentration in lung tissue and the external exposure experienced by each cohort member from whom a lung tissue sample was obtained, the lung tissue data generally confirmed that miners and millers had accumulated substantially greater exposures than the South Carolina textile workers; ratios of the mean lung tissue concentrations for both chrysotile and (separately) amphibole structures agreed well with the ratios of the mean estimates of exposure derived for each of the two cohorts. Thus, Sebastien et al. concluded that the first of the above-listed hypotheses was unlikely to explain the difference in lung cancer potencies observed between the two cohorts. A revised analysis of the data presented by Sebastien et al. (1989) was also conducted by Berman and Crump (2003), with results similarly indicating that the first of the above-listed hypotheses is unlikely to explain the differences in lung cancer potency.

The second of the above-listed hypotheses was addressed both by Sebastien et al. (1989) and by Case et al. (2000). In the first of these, Sebastien et al. suggested that there was little difference in the sizes of structures to which Quebec miners/millers and South Carolina textile workers were respectively exposed. In the second, Case et al. suggested that although a large difference in the sizes of structures

may exist in dusts associated with the two cohorts, the levels of exposures experienced by each cohort suggests that Quebec miners and millers were still exposed to larger absolute numbers of structures of all size ranges. Such findings contrast with those suggested by other published size distributions (Gibbs and Hwang, 1975, 1980; Dement and Harris, 1979; Dement et al., 2007; compared in Berman and Crump, 2003, 2008b).

However, Berman and Crump (2003) describe certain methodological problems with both the Sebastien et al. (1989) and Case et al. (2000) studies that, when addressed, yield findings that are consistent with the other studies (i.e., indicating that textile workers were indeed exposed to substantially longer structures than miners/millers, even in absolute numbers). Because they are central to the focus of the current study, these issues are addressed in further detail in the Discussion section of this paper.

The question of whether a co-carcinogen contributes to the overall observed lung cancer rate among textile workers (the third of the above-listed hypotheses) has been considered by several researchers. To test the hypothesis of whether oils potentially contributed to disease in South Carolina, Dement and Brown (1994) performed a nested case-control study among a subset of the cohort members previously studied by Dement et al. (1994). In this analysis, Dement and Brown qualitatively assessed the probability of mineral oil exposure for cases and controls based on knowledge of historic descriptions of mineral oil use. The extent of such exposure was then further categorized into three strata: none or little, moderate, or heavy, based on where each worker was longest employed. Cases and controls were then further categorized based on years at risk and level of asbestos exposure. Results from this nested analysis indicated no significant change in the estimated exposure-response slope for asbestos after adjusting for mineral oil exposure. Thus, these authors concluded that co-carcinogens are unlikely to explain the difference in lung cancer potency observed between these two cohorts.

Additional, albeit qualitative, evidence that oils may not represent an adequate explanation for the relative lung cancer risks observed in mining and textiles is provided by McDonald (1998b). McDonald suggested that oils were not used in the Rochdale plant until 1974. Therefore, due to latency, it is unlikely that the use of such oils would have had a substantial impact on the observed lung cancer cases at the point in time that studies were conducted in that textile plant (Peto, 1980a, 1980b; Peto et al., 1985).

Note that due to the known interaction between the effects of smoking and asbestos exposure on lung cancer (Hammond et al., 1979; Liddell, 2001; Liddell and Armstrong, 2002; Berry and Liddell, 2004), substantial differences in smoking frequencies between textile workers and miners/millers might also explain the observed difference in asbestos potency toward lung cancer, if such effects were not adequately addressed in the original studies. However, there is little evidence of such effects (Berman et al., 2008a), and as this study is not a formal risk assessment, further consideration of smoking and the other factors addressed above are beyond the intended scope in any case.

Taken as a whole, the evidence presented above suggests that differences in the distribution of structure sizes found in dusts in the textile industry and the mining industry, respectively, is the leading hypothesis for explaining the observed differences in lung cancer risk per unit of exposure between these two industries. As indicated in the previous section, however, existing data suitable for addressing the effects of structure size on lung cancer potency are not sufficient to fully reconcile the difference observed between these two cohorts (Berman and Crump, 2008a, 2008b). Therefore, approaches for reconstructing historical exposures are considered below

Candidate approaches for reconstructing the character of historical dusts

Traditionally, data useful for better characterizing historical exposures were derived from three sources:

1. published size distributions from the relevant study environments;
2. de novo analyses of archived air filters from the relevant study environments; and
3. existing or de novo analyses of lung tissue samples from cohort members and related controls.

However, each approach is associated with unique limitations.

- With the exception of a single study (Dement et al., 2007), data from published size distributions are of limited utility because the longest category of structures separately delineated in the existing studies is "structures longer than 10 μm," whereas the above-cited evidence suggests a need to separately consider structures longer than 20 or even 40 μm to adequately characterize human exposures. Moreover, published distributions typically represent either data from a single sample or pooled data such that only a single distribution is typically reported for any particular environment (reviewed in Berman and Crump, 2003, 2008b). Thus, there is no opportunity for evaluating the sources or magnitude of variation in the published size distributions from the data presented. As a consequence, the findings of Berman and Crump (2008b) may be the best that can be obtained using the currently published data.
- The primary limitation associated with analysis of archived air filters is their availability. Based on personal communications with staff at the National Institute of Occupational Safety and Health (NIOSH) and authors of several of the relevant studies, archived filters may only be available from 3 or 4 of the 25 or so environments of potential interest. Even for those environments, moreover, filters may be available for only very limited time intervals compared to the period over which relevant exposures actually occurred. Fortunately, filters have

been found for one of the two environments of interest for the current study (the South Carolina textile factory), have recently been reanalyzed (Dement et al., 2007), and the unsummarized data were graciously provided by Everett Lehman of NIOSH.

- The primary limitations associated with analysis of cohort-derived lung tissue samples are (1) availability and (2) that the relationship between the internal content of lung tissue and external exposure is complex. Among other things, relating internal dose with external exposure requires consideration of respirability, retention, degradation, and clearance (as summarized, for example, in Berman and Crump, 2003, Chapters 5 and 6). Nevertheless, when the limitations are properly addressed, lung content data have provided unique insight concerning exposure in several studies regarding, for example, the potential effects of structure size (see Discussion) and structure type (Case and Sebastien, 1987, 1989; Case et al., 1997; McDonald et al., 1997).

A candidate approach for providing data to better characterize historical exposures is to apply the Modified Elutriator Method (Berman and Kolk, 1997, 2000) to bulk materials that represent either the feedstocks or products handled in the facilities of interest to generate dusts with characteristics that potentially mimic those of the dusts generated historically during commercial processing of similar materials. As indicated in the following section, a theoretical basis exists that suggests this approach can work. If it does work, moreover, appropriately selected bulk samples can potentially be obtained from virtually every environment of interest. At the same time, questions have been raised concerning the degree with which elutriator-generated dusts from such samples adequately reproduce the character[5] of the historical exposures of interest. Therefore, a major focus of the current study is to evaluate the degree to which elutriator-generated dusts reproduce the character of corresponding historical exposures.

The main features of the Modified Elutriator Method are described in the Background section following the discussion of the theory behind its use for this application.

Factors mediating particle characteristics in dusts (a theoretical basis for using the elutriator)

Whether dusts are generated from disaggregation of asbestos fibrils or disintegration of mineral/rock particles, they are produced by fragmentation that occurs along planes of relative weakness in the starting material and, to the extent that there is regularity in the planes of weakness that results from structural or formational factors, the distribution of particles sizes in the generated dust follows regular patterns that can be modeled (Turcotte, 1986; Wylie, 1993; Wylie and Schweitzer, 1982). Amphiboles, for example, have two planes of weakness inherent in their atomic structure and two additional planes of weakness that sometimes develop during the amphibole formation or subsequent deformation; all four planes are parallel (Ann Wylie, University of Maryland, personal communication). Asbestos fibrils disaggregate along growth boundaries.

The above indicates that as long as commercial processes neither induce chemical reactions that alter chemical composition nor sufficient heating to alter crystalline structure, the character of generated dusts will be determined primarily by the properties of the bulk material processed rather than the nature of the mechanical manipulation to which the materials are subjected. This further suggests that provided the same or highly analogous starting materials are used, reconstruction of the character of historical asbestos exposures by laboratory generation of dusts is possible.

An ore body typically consists of a mixture of components of varying composition with varying properties. Moreover, it is both ore and host rock (when present) that are typically disturbed during mining. Dusts generated by the mechanical processing of these materials will exhibit characteristics (sizes, mineral types, habits[6]) that are a weighted average of the dusts contributed by each of the individual components of the bulk material processed. When the components of bulk materials are separated by classification or other beneficiation, this does not alter the characteristics of individual dusts generated by specific components; it only alters the mix of contributions to the dusts from specific bulk components as the components are separated. Moreover, downstream users of any product (enriched component) would then be exposed only to the dust that is attributable to that specific component. The implication of this is that the nature of dusts to which miners and millers are exposed (generated from weighted mixtures of the components of the ore) should be very different from the nature of dusts generated in factories using specific products that have been classified from the original ore (such as a textile factory using primarily Grade 3 milled fiber).

Given the above, dusts generated in the laboratory from properly selected bulk materials from appropriate stages of commercial operations should allow for reconstruction of the character of dusts to which cohorts studied by epidemiologists were historically exposed.

As the above indicates, the characteristics of the major components of a dust will reflect the major components of the bulk material from which it is derived (e.g., the size of

[5]In this context (and within this study), the term "character of exposure" is intended to mean the size distribution of structures found in the exposure. This is distinct from (and not to be confused with) the intensity (magnitude) of exposure, which the Modified Elutriator Method does not reproduce. Rather, when used in risk assessment, the magnitude of exposure is derived from the exposure estimates of the published epidemiology studies themselves and then linked to the character of exposure either through the PCME fraction of the size distribution in the manner previously described (Berman and Crump, 2008b) or similar procedures suitable for the data that are developed.

[6]A mineral's habit is the crystalline form in which it found. Many minerals occur in multiple crystalline habits, including those that occur in the asbestiform habit (as asbestos); nevertheless, even the asbestos-related minerals primarily occur in nonasbestos habits.

chrysotile structures in a mine dust will be mediated by the properties of the bulk chrysotile in the ore from which it is generated). Thus, as properties of the ore may change spatially within the mine, the characteristics of the dust in the mine may change over time as different sections of the mine are worked. For major components, which will be present at relatively consistent concentrations with limited variability, however, the corresponding characteristics of the dust will also exhibit limited variability. In mining, this will be particularly true of the target mineral, whose processing will be intentionally controlled to satisfy predefined specifications (e.g., the ore needs to be sufficiently rich to be mined economically). Similarly, dusts in a factory processing a feedstock defined by tightly controlled specifications are likely to exhibit only limited variability in the characteristics of their major components. In contrast, trace components that may also be present in an ore (such as intrusions containing tremolite in chrysotile ore—William-Jones et al., 2001) may exhibit occurrences that are quite spatially diverse. Correspondingly, the occurrence of such trace components (e.g., tremolite) in the mine dust, the feedstock shipped to a factory, or the corresponding factory dust may vary radically over time.

As a consequence of the above, dusts from elutriation of a limited number of samples may provide reasonable characterization of the major components of a dust (such as the size of chrysotile fibers in a mine dust or a textile factory dust processing milled chrysotile fiber). In many cases, particularly when the quality of the bulk material processed is tightly controlled to satisfy predefined process specifications, variation may even be sufficiently limited to allow characterization to be reasonably extrapolated across similar facilities. In contrast, the variability of (typically uncontrolled) trace components may vary more substantially so that adequate characterization will require elutriation of a much larger number of samples that are also selected to reasonably represent the time-frame over which characterization is of interest. Thus, as the current study illustrates, it may be reasonable to estimate the size characteristics of structures in an historical chrysotile mine dust or textile factory dust based on elutriation of a limited number of samples. However, extrapolation of any tremolite content observed in elutriated dusts to historical exposures may not be reliable unless a substantially greater number of samples are analyzed and such samples are carefully selected to represent the historical time frame of interest. This is because tremolite is, at most, a minor and uncontrolled components of the materials processed in these cases.

Taken as a whole, these considerations indicate that dusts generated by elutriation of properly selected bulk materials are likely to reproduce the character of dust generated historically from commercial processing of similar bulk materials. This is especially true with regard to the distribution of structure sizes in the dust, although with sufficient data, it may also be possible to develop valid inferences concerning composition by mineralogical type. Notably, the generality with which inferences from elutriated dusts can be extrapolated across materials and environments is a function of the relative degree with which the characteristics of dusts are driven by the properties of bulk materials over the nature of the mechanical manipulation used to process them. Therefore, this issue is also further addressed in this study by conducting a simulation using the unsummarized data from the Dement et al. (2007) study.

About the modified elutriator method

The dust generator developed as part of the Modified Elutriator Method (Berman and Kolk, 1997, 2000) generates dust by tumbling samples of a bulk material in a tumbler through which humidity controlled air is passed to entrain particles liberated from the bulk sample. The air stream is then passed through a custom-designed vertical elutriator[7] (to separate out the respirable fraction) and the dust is collected on filters. The mass of respirable dust deposited on the filters is then determined gravimetrically and the filters can be prepared in any of several ways for analysis of the particulate matter (e.g., by PCM, SEM,[8] TEM, or other analytical techniques).

Analytical results from the Modified Elutriator Method are typically reported as counts of particles of defined size and type per unit mass of respirable dust, although they have also been used (as in the current application) to develop multivariate distributions of the nature of particles in the dusts, in which case, data are reported simply as the number of structures per unit area of filter. For other applications, reporting results typically (as the ratio of particle number to dust mass) has been shown to offer the following advantages:

- these ratios are precisely those required as inputs to published dust emission and dispersion models to cause outputs to be reported as airborne structure-number concentrations that are useful for supporting site risk assessments (Berman and Kolk, 1997, 2000; Berman, 2000);
- estimated airborne structure-number concentrations predicted in the manner described above have been shown to be reasonably accurate for at least two different structure sizes (Berman, 2000); and
- concentrations reported as the indicated ratio of particles to dust have been shown in a limited study to be robust (insensitive) to variations in handling and preparation (grinding) of the bulk sample prior to elutriation (Berman and Kolk, 2000). This is in contrast to most other analytical methods used to report particle concentrations in bulk phases.

[7]A vertical elutriator is simply a circular tube through which air is passed at a controlled velocity equal to the settling velocity of the largest particle of interest (in this case, the largest respirable particle) so that all particles of this size and smaller will rise to the top and be collected on filters, whereas all larger particles will fall to the bottom and be eliminated (Berman and Kolk, 1997, 2000).

[8]Scanning electron microscopy.

The Modified Elutriator Method has been shown to provide good precision (results are highly reproducible) when multiple analyses are conducted on splits of a well-homogenized sample (Berman, 2000, Berman unpublished). The question of whether this method also produces dusts with size distributions that reflect those of historical exposures (when applied to properly selected bulk samples) is addressed in the current study.

Materials and methods

Samples used for elutriation

To represent exposures experienced by miners and millers, three samples of ore stockpiled in 2000 at the Jeffrey Mine, a large open-pit mine in Asbestos, Quebec, were selected for analysis. Similarly, three samples of the 3T-12 milled fiber produced from this same mine between 1964 and 1986 were selected for analysis to represent exposures experienced by textile workers. Note that 3T-12 represents a refined subgrade of Grade 3 milled fiber, which is the grade most commonly employed for fabrication of asbestos textiles. Although the even longer Grades 1 and 2 were also used for manufacture of asbestos textiles, these were never produced in large quantities both because they are rare in ore and because they were hand-cobbed (instead of processed by machine).

Preparation and analysis

Ore samples

The kg-sized ore samples were first sent to a geological laboratory (Centre de technologie minérale et de plasturgie inc. [CTMP]) in Thetford Mines, Quebec, Canada, where they were coarse-crushed (using a jaw crusher) to pass through a 3/8-inch sieve, homogenized, and split to obtain 80-g samples that were then shipped to a laboratory (EMS) in Pasadena, California. In California, respirable-sized dusts generated from these samples using the Modified Elutriator Method (Berman and Kolk, 1997, 2000) were collected on 0.45-μm pore-size (25-mm) mixed cellulose ester (MCE) filters that were then divided and sections from each of four quadrants were prepared and analyzed by PCM using a modified version of NIOSH Method 7400 (NIOSH, 1994a). Also five grids (one from each of the four same quadrants and the center of the filter) were prepared by direct transfer for and analysis by TEM using a modified version of ISO Method 10312 (ISO, 1995).

TEM analyses were conducted using ISO Method 10312 (ISO, 1995). However, the counting and stopping rules were modified (Berman, 2004) to assure adequate precision[9] for structure counts in size categories of interest. Thus, the rules were modified so that a minimum of 50 structures with lengths between 0.5 and 5 μm, 50 structures between 5 and 10 μm, 50 structures between 10 and 20 μm, 100 structures between 20 and 40 μm, and 15 structures longer than 40 μm were counted. Scans for structures shorter than 5 μm were conducted at a magnification of 20,000×, whereas those for longer structures were conducted at 10,000×. The rules were also modified to include all structures with an aspect (length to width) ratio greater than 3 (instead of 5), and although individually enumerated components (of more complex structures) were held at a maximum of 5, an estimate of the total number of such components (beyond 5) were also provided (rather than limiting this estimate to a maximum of 10).

In addition to the mineralogical identification, asbestos structures were characterized morphologically as individual fibers (i.e., single-crystal fibrils or unidentifiable bundles), bundles, clusters, or matrices (all as defined in ISO, 1995). Structures were also characterized as primary (i.e., a structure around which an imaginary boundary can be drawn that crosses no part of the structure and that separates it from all other structures on the viewing screen) or as components of more complex structures.

To facilitate comparison between PCM results and TEM results, structure counts in the same size range as those counted by PCM (NIOSH, 1994a) were also enumerated by TEM. For this study, such PCM-equivalent (PCME) counts were derived using the modified version of ISO Method 10312 (ISO, 1995; Berman, 2004) in which the size definition for PCME from NIOSH Method 7402 (NIOSH, 1994b) was employed. Also, counts of all structures satisfying these dimensional criteria (regardless of composition) were enumerated with the subset of those composed of an asbestos-related mineral separately delineated. Thus, the fraction of asbestos represented by PCME could be determined in a manner fully analogous to that described in NIOSH Method 7402 (NIOSH, 1994b). At the same time, counting PCME as part of the modified ISO 30132 counts assured that such counts were fully comparable with counts of other size fractions.[10]

The minimum precision with which structure dimensions were to be determined was also defined with structure widths determined to two significant figures (i.e., to the nearest 0.05 μm) and structure lengths determined to the nearest 0.3 μm.

Grade 3 samples

The highly fibrous nature of these samples, which resemble cotton in appearance, necessitated that special preparation procedures be adopted; these samples could neither be homogenized nor split in a routine manner (i.e., as

[9]Even allowing for additional subdivision of the size categories defined in the stopping rules, numbers were selected to favor a minimum average count of five structures per category. This means that counts in most categories would be determined to better than a factor of 2. In some cases, however, cost considerations meant that stopping rules had to be relaxed for some samples.

[10]Traditionally, the PCME metric is defined as structures *composed of an asbestos mineral* that satisfy the dimensional requirements for PCM, but are identified by TEM. Therefore, when PCME is used in this paper to indicate all structures satisfying the dimensional requirements (no matter their composition), a subscript will be added to clarify the distinction: PCMEall. PCMEall counts are required, for example, when comparing to PCM counts.

described in Chapter 8 of Berman and Kolk, 2000). To prepare these samples,

- the fibrous material was carefully removed from the sample bag and placed on a preweighed sheet of aluminum foil where its mass was determined to the nearest 0.05 g and it was then teased into eight approximately equal portions;
- a small subsample was then teased out of each of the eight portions (all of approximately equal size) such that their combined mass approximated 5 g. The combined mass was determined and recorded to the nearest 0.05 g. The fraction of fibrous material represented by the combined subsample was also determined as the quotient of its mass to the mass of original material;
- fines remaining in the original sample bag were also quantitatively transferred into a preweighed test tube where the total mass was determined, the tube was sealed and shaken to promote homogenization, and the material was split to obtain a subsample with a mass fraction (relative to the total mass of fines) equal to that of the mass fraction of the subsample of the fibrous material defined above;
- both the subsample of fibrous material and the subsample of fines from the sample were then combined with approximately 50 g of washed play sand and the mixture was placed in the tumbler of the dust generator/elutriator to generate respirable dust using the Modified Elutriator Method (Berman and Kolk, 2000).[11]

Because these Grade 3 samples were originally to be analyzed for a different objective than that of the current study (Berman, 2004), respirable dust samples generated from these samples were initially collected on 0.4-μm pore-size (25-mm) polycarbonate (PC) filters, which allowed their mass to be determined with high precision but precluded analysis by PCM. Therefore, additional material from two of the three samples (the third could not be located) were recently reprepared and new respirable dust samples were generated and collected on MCE filters using the Modified Elutriator Method for the express purpose of deriving comparable PCM and TEM analyses (for PCME structures only). However, other than requiring this separate and additional analysis, the procedures employed for PCM and TEM analysis of these samples were identical to those described above for the ore samples.

Other data used to characterize factory dusts

To evaluate the performance of the dust generator/elutriator, TEM-derived size distributions[12] of factory dusts from the published literature were compared to the size distributions generated by elutriation in this study. Ideally, such data would contain a broad range of size categories to allow for the richest comparison, although this was not always the case.

Based on the set of published distributions previously identified (Berman and Crump, 2008b), candidate distributions potentially applicable to the Quebec mining environment include those from Gibbs and Hwang (1980) and Winer and Cossett (1979). Candidate distributions for the South Carolina textile facility are found in Cherrie et al. (1987), Dement and Harris (1979), and Dement et al. (2007). Of these, Cherrie et al. was eliminated from further consideration because the longest cut point available from this study is all structures longer than 5 μm, which would severely limit pertinent analysis. Similarly, data from Winer and Cossett are eliminated from further consideration because they are based only on a very small number of structure counts and, of these, only a handful are longer than 5 μm. The remaining distributions are described below.

Dement et al. (2007)

Dement et al. analyzed 84 sample filters representing a stratified random subset of 203 filters collected at the South Carolina textile plant during NIOSH surveys conducted between 1964 and 1968. These samples were analyzed by TEM using a modified version of ISO Method 10312 (ISO, 1995). Modifications incorporated for these analyses were

- including all fibers and bundles with aspect ratios greater than 3 (rather than limiting counts to those with aspect ratios greater than 5);
- sizing structures solely by assigning them to preselected categories (rather than providing precise values for the lengths and widths of each individual structure). For the specific categories enumerated, diameters were recorded in increments of 0.25 μm and lengths in increments of 0.5 μm (for lengths up to 5 μm) and 1 μm (for lengths greater than 5 μm)[13];
- counting all fibers and bundles (using the morphological definitions in the ISO method for both) whether

[11]Use of washed play sand is a standard procedure described in the method (Berman and Kolk, 2000). It promotes stable emission of dusts during tumbling and elutriation. Prior to mixing, "sand blanks" are run in the elutriator to assure that it will contribute no asbestos and no more than inconsequential amounts of respirable dust to the filters collected from actual samples.

[12]The published distributions were derived from analysis of air-sample filters that were collected from facilities of interest. Though typically collected over a relatively short time interval, such samples represent dusts actually generated by commercial processing at each particular facility.

[13]A further complication described for this study (Dement et al., 2007; John Dement personal communication) was that the size boundaries for these categories were originally set assuming a target (ideal) magnification, rather than accounting for the actual magnifications under which the analyses were completed. The consequence of this is that the size boundaries for the categories are not precisely "as advertised" so that (at least) a small number of structures have potentially been misclassified by placing them in the wrong category. In such cases, however, such structures would have been placed in categories for sizes contiguous with the category representing the correct size. Except for those categories with relatively few structures, the effect of this consideration on overall size distributions may be relatively limited and has been further ameliorated by at least partially addressing the effect during extraction of summarized information from the original, unsummarized data (John Dement, Kenny Crump, personal communication).

observed as primary structures or components of more complex structures (rather than limiting individual enumeration of components to five structures); and
- stratifying counts (much as was also done in the present study, but using different strata) to increase the precision of the counts of the longest structures. Dement et al. divided counts into the following strata:
  - structures longer than 0.5 μm;
  - structures longer than 5 μm; and
  - structures longer than 15 μm.

Multiple samples were analyzed from each of 10 exposure units (processing areas) of the South Carolina factory and (in the published study) results from all samples within each exposure unit were combined to provide an overall zone-specific bivariate distribution. However, facilitated by access to the unsummarized data, in the present study, size distributions in this study were separately generated for each of the individual samples analyzed by Dement and coworkers using the same statistical procedures employed to generate size distributions from the elutriated Grade 3 and ore data analyzed in this study (see "Statistical Methods" below).

Note that to save time, the data used for this study were extracted from a master data file developed by Kenny Crump (Louisiana Technical University), which was previously extracted from the multiple files of the original data set and refined and corrected with the assistance of John Dement as part of an ongoing, three-way collaboration.

Dement and Harris (1979)

Dement and Harris analyzed filters from personal air samples collected by NIOSH at various facilities including an asbestos textile factory (likely the South Carolina facility) between approximately 1971 and 1977. Samples were collected on 37-mm MCE filters (pore size not indicated). For the textile facility, 20 samples were analyzed from each of three process areas: fiber preparation, twisting, and weaving and filters were analyzed both by PCM, using the then current NIOSH criteria for a recommended standard (NIOSH, 1972), and by TEM (no method cited) following preparation using a direct transfer procedure (Zumwalde and Dement, 1977). TEM determinations were made at magnifications between 10,000× and 17,000×. Bivariate size data are reported as the number of enumerated "fibers" in each size category (with category dimensions defined by the midpoints of their respective lengths and widths and categories representing the largest dimensions left unbounded). Fiber counts in each category were presumably summed over the fibers observed on each sample in each process area. Based on this assumption, the data were converted in this study to relative size distributions simply by dividing the indicated fiber counts by the total number of fibers reported.

Although it is stated that the structures counted are "fibers" with aspect ratio ≥3, the authors provide no other morphological information (indicating such things, for example, as whether bundles were delineated or included or whether both primary and component fibers were included). The authors note that fiber diameter was defined as the maximum transverse dimension (as opposed to the more common: average transverse dimension) and that length was defined as the maximum chord of a circle containing the fiber. Lacking definitive information on morphology, it was assumed for this evaluation that the structures counted represent the equivalent of "total fibers and bundles," which in this study indicates counts of all fibers and bundles, whether they represent primary structures or components of more complex structures.

Because only published (summarized) data are available for this study, comparisons were restricted to the size categories presented in the published study. Moreover, having access only to the single, pooled summaries, which precludes the ability to evaluate the variability associated with the size distributions reported, comparisons were restricted to visual evaluation (see Statistical Methods below).

Gibbs and Hwang (1980)

Gibbs and Hwang analyzed area samples of airborne dusts collected from various process areas of the mines and mills of Quebec and South Africa. Samples were collected on PC and MCE filters (neither pore size nor diameter reported). PC filters were analyzed by SEM and MCE filters were analyzed by TEM (no method cited) following preparation by direct transfer. Although Gibbs and Hwang apparently counted and sized hundreds of fibers, results are reported simply as the relative fraction of fibers in each of the size categories of the bivariate table provided in the paper. Both the lower and upper ends of the range of dimensions included in each category are indicated in the bivariate table with both the smallest and largest categories unbounded in the extreme direction.

One severe limitation placed on these data is that the maximum width cut point reported by Gibbs and Hwang is 0.3 μm, although based on figures of the continuous distributions provided in their paper, this could be extended to a maximum cut point of 0.4 μm (Berman and Crump, 2008b). Nevertheless, this limitation restricted the range of size categories that could be compared with the data from the current study.

Because little morphological information is provided in this study, to further the present analysis, it is assumed that the structures counted by Gibbs and Hwang most closely compare to counts of total fibers and bundles in the present study, although this is not known with certainty. Moreover, as no information from which to evaluate the variability of this distribution was provided, comparisons were restricted to visual evaluation (see "Statistical Methods" below).

Statistical methods

To promote comparability, both the elutriated data from this study and the unsummarized data from archived air samples collected at the South Carolina textile plant were summarized and evaluated using the same procedures, which are described below. Note, however, as the number of structures

counted on the South Carolina samples was defined at the time of analysis (Dement et al., 2007), the precision of these data were fixed at that time and differ somewhat from the precision achieved for specific size categories among the elutriated data from the present study. The effects of this difference in precision are explicitly addressed in the manner described in the Results section.

Estimating relative abundance

Size distributions (i.e., estimates of the relative fraction of total structures represented by each size category of interest) were determined in the following manner.

For each sample filter, i, let

A_{ji} = the relative area of the ith filter examined for structures in the jth size category (arbitrary units);

n_{ji} = the number of structures in the jth size category on the ith filter (number);

λ_{ji} = the density of the jth size category of structures on the ith filter (str/unit area);

λ_i = the density of all structures on the ith filter (str/unit area); and

f_{ji} = the fraction of all structures that are in the jth size category on the ith filter (unitless).

Values for the λ's and the f_{ji}'s were then estimated for each filter as follows:

$$\lambda_{ji} = \frac{n_{ji}}{A_{ji}} \tag{1}$$

$$\lambda_i = \sum_j \lambda_{ji} \tag{2}$$

$$f_{ji} = \frac{\lambda_{ji}}{\lambda_i} \tag{3}$$

Estimates of the fraction of all structures in the jth size category, f_j, among pooled samples were estimated as

$$f_j = \frac{\sum_i f_{ji} \times \lambda_i}{\sum_i \lambda_i} \tag{4}$$

Samples were pooled, for example, to derive estimates of the general size distributions for Grade 3 milled fiber, chrysotile ore, exposure zones within the South Carolina textile factory, and the textile factory as a whole.

Comparing structure size distributions

Although dictated by the size categories reported in other studies, matched sets of size categories could be constructed to allow comparison between the size distributions generated by elutriation in this study and all of the published distributions of interest.

Depending on the specific objectives of each analysis and the quality of the available data, comparisons between size distributions were conducted using one of three approaches. When the goal was to compare distributions from individual samples (or to search for differences between individual samples among different sample sets), a contingency table analysis was employed. For such analyses, the observed number of structures in each size category of each sample, n_{ji}, was paired with its corresponding expected value for these counts, ne_{ji}.

In a traditional contingency table analysis, expected values are determined for each category of each sample as the product of the sum of counts across size categories for that sample i and the sum across samples of counts for that size category j divided by the total number of structures in all size categories of all samples:

$$ne_{ji} = \frac{\sum_j n_{ji} \times \sum_i n_{ji}}{\sum_i \sum_j n_{ji}} \tag{5}$$

However, because the relative area of each filter scanned for each size category was not the same across samples, this traditional procedure for developing estimates of expected values for a contingency table test could not be used. Instead, expected values are determined as the product of f_j (the fraction of structures in each size category derived from the pooled data; Equation 4), λ_i, and the area of the filter scanned, A_{ji}:

$$ne_{ji} = f_j \times \lambda_i \times A_{ji}. \tag{6}$$

By rewriting Equation 5 as

$$ne_{ji} = \frac{\sum_j n_{ji}/A_{ji} \times \sum_i n_{ji}/A_{ji}}{\sum_i \sum_j n_{ji}/A_{ji}} \times A_{ji}$$

and substituting Equations 1, 2, 3, and 4 into Equation 6, it can be seen that Equations 5 and 6 are equivalent, as long as equivalent areas are scanned across samples. Correspondingly, Equations 5 and 6 provide consistent estimates for expected values as long as the areas scanned for each size category are equivalent across samples. Equation 6 also provides estimates for expected values that do not vary when different areas are scanned for specific size categories on different samples, as long as the ratio of counts to area for each size category of each sample remains constant. This is precisely the behavior required for the analyses conducted in this study.

A chi-square statistic was then calculated for the sample set and the p value determined from a chi-square distribution with $(i-1)\times(j-1)$ degrees of freedom. Note that size categories for which expected values were calculated as zero were necessarily excluded from the analysis, which would correspondingly reduce the number of degrees of freedom.

When the goal of a comparison was to identify differences between sample sets beyond what was otherwise attributable to the variation in the individual samples of each set, Mann-Whitney rank-sum tests (Devore, 2004) were employed. To apply a Mann-Whitney, the concentration of structures in each size category of interest was first calculated for each sample. These concentrations were then

divided by the concentration of a reference size (chosen to be the PCME fraction for reasons described in "Results"). Note that dividing by a reference category eliminates (normalizes for) the effects of variation in loading across the samples. Separate p values were then determined independently for each size category of interest.

Finally, due to limitations in published data, the formal statistical approaches described above could not generally be applied to compare published (summarized) distributions with those derived in this study. Therefore, such size distributions were presented as bar charts and compared visually. This approach was required, for example, when comparing elutriator data to the summarized factory data from Dement and Harris (1979) or Gibbs and Hwang (1980). In contrast, because we had access to the raw (unsummarized data) from Dement et al. (2007), the more formal statistical procedures describe above were used in the comparison with elutriated data. The more formal procedures were also used when comparing between sample sets of elutriated data from different environments.

Considering size and analytical technique in risk assessment

Although questions of risk are not formally addressed in this study, one goal is to evaluate whether distinctions in size distributions are potentially sufficient to explain observed disparities in potency factors between cohorts of textile workers and chrysotile miners/millers. Consequently, the manner in which structure size can be incorporated for consideration in risk equations is addressed here to develop a target criterion against which the effects of differences in structure sizes experienced by each cohort can be judged.

Importantly, differences in structure size potentially affect potency in two ways. The first and most obvious is that structures of different sizes may be differentially potent (Berman and Crump, 2008b) so that the differences in size distributions observed by TEM need to be evaluated. The second involves effects that size distributions have on the relationship between concentrations determined by PCM (the technique traditionally used to determine asbestos concentrations that are reported by epidemiologists) and TEM (the analytical technique required to adequately delineate size distributions). This ratio of such measurements (i.e., the ratio of the PCM/PCME metrics, as defined under preparation and analysis and further described below) is used to link size distributions to the original epidemiology data (see Berman and Crump, 2003, 2008b). Therefore, both effects are addressed here.

In the earlier meta-analysis (Berman and Crump, 2008b), the risk equation for lung cancer was expanded so that it could accommodate exposure metrics incorporating structure size categories other than PCM. In that formulation, concentrations determined by PCM, C_{PCM}, were assumed to be equivalent to concentrations determined for the same metric, when analyzed by TEM (the PCME metric), C_{PCME}. Thus, the relationship between the lung cancer potency factor, K_L, (determined using PCM) and adjusted potency factors, $K_{L_i}^*$, for each of a potential series of i structure size categories (determined using TEM) was expressed as

$$K_L \times C_{PCM} = K_L \times C_{PCME} = \sum_i \left(K_{L_i}^* \times C_i\right). \quad (7)$$

Recognizing that concentrations for any structure size category i (including PCME) determined by TEM can be expressed as the product of the fraction of structures in the indicated size category and the concentration of total structures,

$$C_i = f_i \times [Conc\ of\ Total\ Structures],$$

the relationship between the original potency factor and potency factors for other size categories was then expressed as

$$K_L = \sum_i K_{L_i}^* \times \left[\frac{f_i}{f_{PCME}}\right]. \quad (8)$$

The meta-analysis conducted in the earlier paper relied on published data from which it was not possible to evaluate the relationship between PCM and PCME. Hence, the two types of measurements were assumed to be equivalent. In the current study, however, it was possible to analyze the same sample filters using both PCM and TEM. Thus, the relationship between PCM and PCME was directly determined. As a result, the equations presented here are further modified to allow explicit consideration of differences between PCM and PCME.

If the potency factors are labeled to indicate the metric to which they are linked, the left-side equality from Equation 7 yields

$$K_{LPCM} \times C_{PCM} = K_{LPCME} \times C_{PCME}.$$

Dividing both sides by C_{PCME} generates

$$K_{LPCM} \times \left[\frac{C_{PCM}}{C_{PCME}}\right] = K_{LPCME}. \quad (9)$$

Recognizing that K_L in Equation 8 should also be labeled as K_{LPCME}, substituting Equation 8 into Equation 9, and rearranging yields the following relationship, which can be used to evaluate the effects of differences in both measurement techniques (i.e., PCM versus PCME by TEM) and structure size on potency,

$$K_{LPCM} = \sum_i K_{L_i}^* \times \left[\frac{f_i}{f_{PCME}}\right] \times \left[\frac{C_{PCME}}{C_{PCM}}\right]. \quad (10)$$

In the companion paper to the meta-analysis, Berman and Crump (2008a) present a series of lung cancer potency estimates from various published epidemiology studies. Based on the list presented in Table 3 of that paper, it can be seen that the K_L derived from the South Carolina textile manufacturing cohort is approximately 47 times the value estimated for the cohort of chrysotile miners and millers. Combining this observation with the relationship indicated in Equation 10, the following relationship can be used to

explore the potential effects of structure size and analytical technique on estimates of lung cancer potency in this study:

$$47 = \frac{K_{LPCM(G3)}}{K_{LPCM(Ore)}} = \left\{\frac{\sum_i K^{\bullet}_{L_i G3}}{\sum_i K^{\bullet}_{L_i Ore}}\right\} \times \left\{\frac{\left[\frac{f_i}{f_{PCME}}\right]_{G3}}{\left[\frac{f_i}{f_{PCME}}\right]_{Ore}} \times \frac{\left[\frac{C_{PCME}}{C_{PCM}}\right]_{G3}}{\left[\frac{C_{PCME}}{C_{PCM}}\right]_{Ore}}\right\} \quad (11)$$

In Equation 11, the potency factors for textile workers (who used primarily Grade 3 milled fiber as a feedstock) are in the numerator and the potency factors for miners (who were exposed to ore) are in the denominator. As the entire ratio equals 47, if the adjusted potency factors (the $K^{\bullet}_{L_i}$) for textile workers and miners are to be reconciled (made equivalent), then the product of the two ratio of ratios to the right of the ratio of adjusted potency factors in Equation 11 needs to approach a value of 47. Equation 11 thus provides a criterion against which the ability of candidate exposure metrics to reconcile the differences in potencies between these two cohorts can be evaluated.

Evaluating differences across exposure zones

As previously indicated, the size distributions reported by Dement et al. for the South Carolina factory were generated by grouping the 84 available samples into categories representing each of the 10 zones within the factory from which they were collected and pooling the structure counts within each zone (details provided in Dement et al., 2007).

To test various hypotheses concerning potential differences in size distributions between zones, a simulation (randomization test; McDonald, 2009) was conducted in this study in which 83 samples from the South Carolina plant (data from one sample was lost) were randomly regrouped into 10 new "hypothetical" zones and the variation between the groups determined (by calculating the variance across zones within each size category that was evaluated). The random regrouping of samples was then repeated 1000 times and the distribution of variation across the zones (within each size category) was determined. The percentiles of this distribution were then compared to the variance observed in the original grouping of the samples into the 10 zones reported by Dement et al. (2007).

This exercise was conducted to partially evaluate the theoretical bases supporting use of the elutriator to reconstruct historical exposures. As described in the Background section, if dust characteristics are driven primarily by the properties of the bulk materials from which they are derived, rather than the nature of mechanical processes applied to such materials, then the characteristics of laboratory-generated dusts (using the elutriator) should reasonably reproduce the character of field-generated dusts, as long as the same (or similar) bulk materials are used in both places to generate the dusts. The simulation test was applied to the Dement et al. data to distinguish among factors that mediate dust characteristics.

Results

Because it is easier to illustrate the approaches used for statistical analysis and interpretation in this study with elutriator data than with published data, the comparison between elutriated samples of Grade 3 (representing textile dusts) and ore (representing mine dusts) to address the *second* objective of the study is presented first and this is followed by comparisons between the elutriated dusts and the published size distributions to address the *first* objective of this study; it is fully recognized that findings based on comparisons among elutriated dusts cannot be considered valid until the ability of the elutriator to adequately reproduce the character of historical exposures is confirmed through comparisons between elutriated dusts and published data (representing the character of dusts collected during commercial processing of the same or similar materials as what is elutriated).

Comparisons between elutriator-generated dusts from Grade 3 milled fiber and Quebec ore

Results from analyses of three Grade 3 dust samples (1R1, 3R1, and 5R1) and three ore dust samples (34c, 38c, and 43d) are presented in Table 1. In this table, the number of fibers and bundles observed in each sample (top of table), the relative area scanned on each sample filter (middle), and the relative abundance of fibers and bundles in each of the indicated size categories (i.e., the size distribution) in each sample (bottom) are presented. Separate sets of results are provided for primary fibers and bundles alone or total fibers and bundles (which also include those that are components of more complex structures). Estimates of the pooled frequencies of Grade 3 structures (determined by combining the data from all three Grade 3 samples) and, separately, the ore samples are also presented (bolded rows).

It is apparent from the relative frequencies of structures reported in Table 1 that each of the Grade 3 samples differs somewhat from one another (as do the ore samples). However, the differences between the two groups of samples are substantially greater, with ore dusts exhibiting increased concentrations of short structures (length < 5 μm) relative to Grade 3 dusts and, conversely, Grade 3 dusts being enriched in longer structures. For the same length, structures in Grade 3 dusts are also thinner than those from ore, although this difference becomes less pronounced as the length of the structures increases. Such observations become even clearer when the relative frequencies are graphed (Figure 1).

As can be seen in Figure 1 (for total fibers and bundles), despite the variation observed within sample types, differences between sample types (Grade 3 and ore) are clear and obvious. Moreover, although not shown, a similar figure was constructed for primary fibers and bundles alone. Because this latter figure exhibits somewhat less variation within sample types, the differences between sample types are even more clear and obvious.

Table 1. Number and fraction of fibers and bundles in elutriated samples of GRADE 3 milled fiber and raw ore from Quebec.

		Size categories (μm)																			
		L≤5				5<L≤10				10<L≤20				20<L≤40				40<L			
Sample type	Sample ID	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W
Number of Primary Fibers and Bundles Counted During Analysis																					
Grade 3	1R1	120	8	14	0	52	8	15	0	105	34	35	21	33	34	30	14	6	11	11	1
	3R1	148	10	8	0	39	2	4	2	149	48	53	22	59	35	42	6	7	7	9	1
	5R1	159	12	8	0	29	5	14	1	178	35	100	29	49	20	53	17	6	10	11	1
Ore	34c	19	1	3	0	16	3	13	4	19	1	16	6	32	14	18	8	11	1	9	3
	38c	24	0	1	0	6	1	11	2	11	2	14	4	17	7	14	5	3	3	4	0
	43d	35	2	0	0	8	1	13	4	4	4	11	9	13	5	16	27	4	3	6	8
Number of Total Fibers and Bundles (including those that are components of more complex structures)																					
Grade 3	1R1	162	10	15	0	57	8	15	0	110	35	36	21	34	34	30	14	6	11	11	1
	3R1	172	10	9	0	43	2	5	2	150	48	53	22	60	35	42	6	7	7	9	1
	5R1	204	14	8	0	36	5	15	1	191	38	101	29	53	20	53	17	6	10	11	1
Ore	34c	55	1	4	0	31	5	26	5	30	2	18	6	51	20	22	10	14	1	12	3
	38c	49	1	2	0	21	2	23	5	46	7	20	5	61	16	26	9	7	7	7	0
	43d	67	3	0	0	26	5	20	4	26	8	17	13	35	13	31	29	6	5	8	8
Relative Area of Filter Scanned During Analysis (Arbitrary Units)—Note that the same areas of each sample filter were scanned whether counting primary or total structures																					
Grade 3	1R1	0.047	0.047	0.047	0.047	0.113	0.113	0.113	0.113	1.758	1.758	1.758	1.758	1.758	1.758	1.758	1.758	1.758	1.758	1.758	1.758
	3R1	0.047	0.047	0.047	0.047	0.085	0.085	0.085	0.085	1.335	1.335	1.335	1.335	1.335	1.335	1.335	1.335	1.335	1.335	1.335	1.335
	5R1	0.047	0.047	0.047	0.047	0.075	0.075	0.075	0.075	0.771	0.771	0.771	0.771	0.771	0.771	0.771	0.771	0.771	0.771	0.771	0.771
Ore	34c	0.001	0.001	0.001	0.001	0.056	0.056	0.056	0.056	0.166	0.166	0.166	0.166	0.902	0.902	0.902	0.902	0.902	0.902	0.902	0.902
	38c	0.001	0.001	0.001	0.001	0.056	0.056	0.056	0.056	0.194	0.194	0.194	0.194	1.335	1.335	1.335	1.335	1.335	1.335	1.335	1.335
	43d	0.001	0.001	0.001	0.001	0.065	0.065	0.065	0.065	0.360	0.360	0.360	0.360	2.172	2.172	2.172	2.172	2.172	2.172	2.172	2.172
Fraction of Primary Fibers and Bundles in Each Indicated Size Category (determined as described in Materials and Methods)																					
Grade 3	1R1	0.6586	0.0439	0.0768	0	0.1189	0.0183	0.0343	0	0.0154	0.0050	0.0051	0.0031	0.0048	0.0050	0.0044	0.0021	0.0009	0.0016	0.0016	0.0001
	3R1	0.7131	0.0482	0.0385	0	0.1044	0.0054	0.0107	0.0054	0.0253	0.0081	0.0090	0.0037	0.0100	0.0059	0.0071	0.0010	0.0012	0.0012	0.0015	0.0002
	5R1	0.6607	0.0499	0.0332	0	0.0753	0.0130	0.0364	0.0026	0.0451	0.0089	0.0253	0.0073	0.0124	0.0051	0.0134	0.0043	0.0015	0.0025	0.0028	0.0003
Pooled Grade 3		**0.6773**	**0.0476**	**0.0476**	**0**	**0.0975**	**0.0120**	**0.0273**	**0.0028**	**0.0300**	**0.0075**	**0.0141**	**0.0049**	**0.0094**	**0.0053**	**0.0087**	**0.0026**	**0.0012**	**0.0018**	**0.0020**	**0.0002**
Ore	34c	0.8026	0.0422	0.1267	0	0.0081	0.0015	0.0066	0.0020	0.0032	0.0002	0.0027	0.0010	0.0010	0.0004	0.0006	0.0003	0.0003	3E-05	0.0003	9E-05
	38c	0.9401	0	0.0392	0	0.0040	0.0007	0.0073	0.0013	0.0021	0.0004	0.0027	0.0008	0.0005	0.0002	0.0004	0.0001	8E-05	8E-05	0.0001	0
	43d	0.9336	0.0533	0	0	0.0031	0.0004	0.0051	0.0016	0.0003	0.0003	0.0008	0.0006	0.0002	0.0001	0.0002	0.0003	5E-05	4E-05	7E-05	9E-05
Pooled Ore		**0.8897**	**0.0354**	**0.0545**	**0**	**0.0051**	**0.0009**	**0.0062**	**0.0017**	**0.0018**	**0.0003**	**0.0020**	**0.0008**	**0.0005**	**0.0002**	**0.0004**	**0.0002**	**0.0002**	**5E-05**	**0.0002**	**7E-05**

Table 1. continued on next page

Table 1. Continued.

		Size categories (μm)																			
		L≤5				5<L≤10				10<L≤20				20<L≤40				40<L			
Sample type	Sample ID	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W	W<0.25	0.25≤W <0.4	0.4≤W <1.5	1.5≤W
Fraction of Total Fibers and Bundles (including those that are components of more complex structures)																					
Grade 3	1R1	0.7059	0.0436	0.0654	0	0.1035	0.0145	0.0272	0	0.0128	0.0041	0.0042	0.0024	0.0040	0.0040	0.0035	0.0016	0.0007	0.0013	0.0013	0.0001
	3R1	0.7307	0.0425	0.0382	0	0.1015	0.0047	0.0118	0.0047	0.0224	0.0072	0.0079	0.0033	0.0090	0.0052	0.0063	0.0009	0.0010	0.0010	0.0013	0.0001
	5R1	0.6940	0.0476	0.0272	0	0.0765	0.0106	0.0319	0.0021	0.0396	0.0079	0.0210	0.0060	0.0110	0.0041	0.0110	0.0035	0.0012	0.0021	0.0023	0.0002
Pooled Grade 3		**0.7090**	**0.0448**	**0.0422**	**0**	**0.0924**	**0.0100**	**0.0243**	**0.0023**	**0.0262**	**0.0065**	**0.0118**	**0.0041**	**0.0082**	**0.0044**	**0.0073**	**0.0021**	**0.0010**	**0.0015**	**0.0017**	**0.0002**
Ore	34c	0.8997	0.0164	0.0654	0	0.0061	0.001	0.0051	0.001	0.002	0.0001	0.0012	0.0004	0.0006	0.0002	0.0003	0.0001	0.0002	1E-05	0.0001	4E-05
	38c	0.9185	0.0187	0.0375	0	0.0067	0.0006	0.0073	0.0016	0.0042	0.0006	0.0018	0.0005	0.0008	0.0002	0.0003	0.0001	9E-05	9E-05	9E-05	0
	43d	0.9432	0.0422	0	0	0.0053	0.001	0.0041	0.0008	0.001	0.0003	0.0006	0.0005	0.0002	8E-05	0.0002	0.0002	4E-05	3E-05	5E-05	5E-05
Pooled Ore		**0.9191**	**0.0257**	**0.0364**	**0**	**0.006**	**0.0009**	**0.0053**	**0.0011**	**0.0022**	**0.0003**	**0.0012**	**0.0004**	**0.0005**	**0.0002**	**0.0003**	**0.0001**	**0.0001**	**4E-05**	**0.0001**	**3E-05**

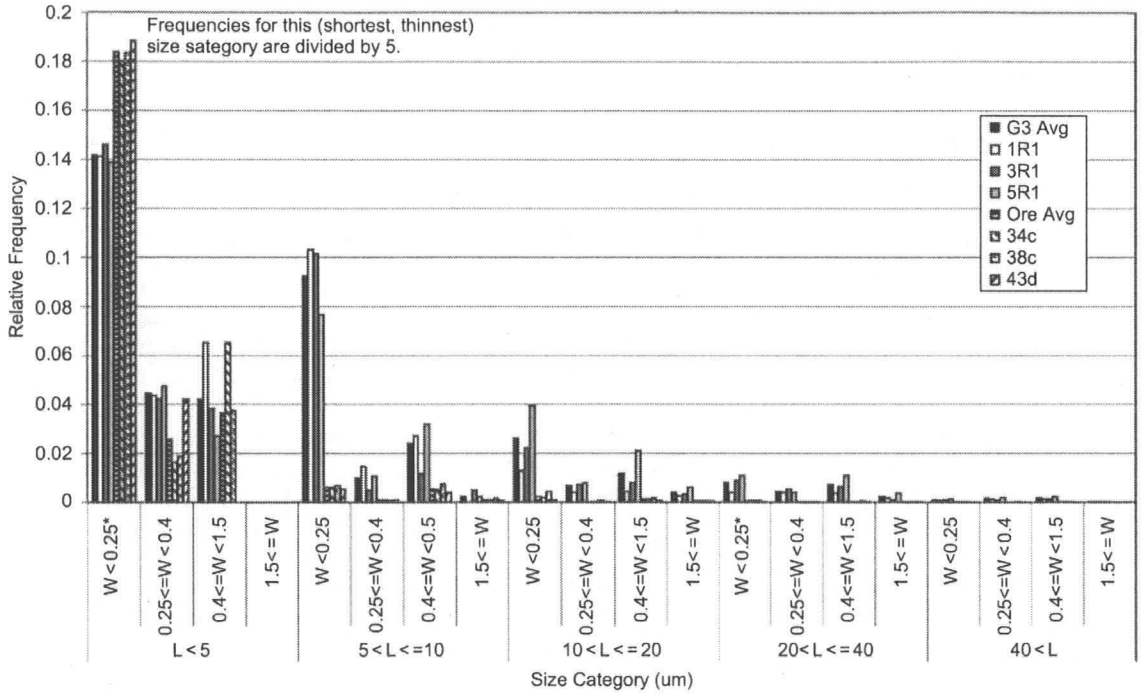


Figure 1. Individual and "averaged" (pooled) size distribution in dusts generated by elutriation from samples of Grade 3 and Quebec ore (total fibers and bundles).

It should also be noted in Figure 1 that the relative frequencies of structures in all samples for the size category containing the shortest and thinnest structures (length < 5 μm and width < 0.25 μm) were divided by a factor of 5 so that the relative frequencies in all other size categories could be reasonably compared on the same figure. Thus, for comparison across size categories, it needs to be remembered that structures in the shortest/thinnest size category are 5 times more abundant than indicated by the sample bars (as noted in the figure).

Findings suggested in Table 1 and Figure 1 were also evaluated statistically using contingency-table analyses. Results are summarized in Table 2, which also presents the summed chi-square statistics for each test and the number of degrees of freedom. As can be seen by the *p* values presented in the right-most column of the table, differences between individual samples among each group tested (Grade 3, ore, or both combined) are all highly significant.

That the individual samples of dust from ore and, separately, Grade 3 are different from one another suggests that the characteristics of the ore deposit varies spatially in the mine, which then translates into temporal variation in the mined ore and the milled-fiber products. Consequently, to properly distinguish between the characteristics of ore dusts and Grade 3 dusts, the Mann-Whitney test was adopted because it is sensitive to variation between sample sets that is beyond what is observed within the sample sets (see "Materials and Methods"). As previously indicated, the Mann-Whitney test is applied to ratios of size categories, which removes the effects of differences in loading between the sample filters being compared. Because ratios of structure sizes of interest to phase-contrast microscopy equivalent (PCME) concentrations have previously been applied to test risk-related hypotheses (e.g., Berman and Crump, 2008b), the size category corresponding to PCME structures was also chosen as the denominator for these ratios here.

Table 2. Contingency table tests comparing size distributions in eluatriated dusts for Grade 3, raw ore, and both combined.

Sample set	Degrees of freedom	Sum chi-square	*p* value	Significantly different?
Primary Fibers and Bundles				
Grade 3[a]	36	269	1.7E-37	Yes
Ore[b]	36	150	6.3E-16	Yes
All combined[c]	90	6678	0	Yes
Total Fibers and Bundles				
Grade 3[a]	36	285	1.4E-40	Yes
Ore[b]	36	156	7.2E-17	Yes
All combined[c]	90	9666	0	Yes

[a]These are tests to determine whether individual samples of Grade 3 milled fiber are different from one another.
[b]These are tests to determine whether individual samples of ore dusts are different from one another.
[c]These are tests to determine whether Grade 3 dusts and ore dusts are different from one another.

The mechanics used to apply the Mann-Whitney test to structure size categories in this study are illustrated in Table 3. On the left side of this table, ratios are presented that are derived by dividing the relative frequencies of the indicated size categories by the relative frequency of the size category represented by PCME structures. The right side of

the table presents the relative ranks of these ratios for each of the six indicated samples. At the bottom on the right are the sums of the ranks for Grade 3 samples along with the corresponding *p* values from the Mann-Whitney test. As can be seen by the ranks, these two sample sets differ as extremely as possible (i.e., one sample set exhibits all of the lowest ranks and the other all the highest) for all of the size categories listed, except for the category with length > 10 μm. The ranks for this last size category exhibit the second most extreme possible among six samples, which (when comparing sets of three samples each) is not significant.

Based on the results in Table 3, dusts generated in the laboratory from Grade 3 milled fiber and raw ore are significantly different and, based on the direction of the ranks, structures in the dusts from ore are significantly shorter. These findings are entirely consistent with those reported from the contingency table analysis, except that differences within sample sets have now been addressed. It is also noteworthy that this analysis demonstrates that the differences between Grade 3 and ore dusts can be delineated with as few as three samples each.

To better elucidate the detailed distinctions between Grade 3 and ore dusts, results of applying the Mann-Whitney test to the full set of size categories identified in Table 1 are summarized in Table 4. However, the format for Table 4 has been modified to emphasize both the results of the Mann-Whitney test (top half of table) and the magnitude of the ratios of the relative frequencies observed between Grade 3 and ore dusts for each (corresponding) size category (bottom half of table). As can be seen in Table 4, whether one considers total fibers and bundles or primary structures alone, differences between ore and Grade 3 dusts are significant for nearly half of the size categories presented in the table.

It can also be seen in Table 4 that it is generally the ratios of size categories containing longer structures (length > 10 μm) that are greater than one, which is what is required

Table 3. Comparison of the characteristics of elutriated dust samples generated, respectively, from Grade 3 milled fiber and raw ore from Quebec[a]

		Structure ratios[b]					Ratio ranks[c]				
	Lengths:	<5	>5	>10	>20	>40	<5	>5	>10	>20	>40
	Widths:	All[d]	All	All	All	All	All	All	All	All	All
Sample ID	Sample type										
1R1	Grade 3	12.823	2.904	0.618	0.255	0.051	5	2	4	3	3
3R1	Grade 3	15.068	3.487	1.208	0.456	0.067	4	1	1	1	1
5R1	Grade 3	7.545	2.260	1.071	0.344	0.057	6	3	2	2	2
34c	Ore	102.617	1.926	0.550	0.164	0.038	2	4	5	4	4
38c	Ore	73.503	1.893	0.668	0.132	0.021	3	5	3	5	5
43d	Ore	124.996	1.834	0.399	0.096	0.020	1	6	6	6	6
Sum of ranks[e]							15	6	7	6	6
p value[f]							.05	.05	.1	.05	.05

[a]These are dusts generated as described in the Modified Elutriator Method (Berman and Kolk, 1997, 2000).
[b]These are the ratios of concentrations of primary fibers and bundles in the indicated size categories divided by concentrations of PCM-equivalent fibers and bundles (with dimensions L > 5 μm and 0.25 μm < W < 3 μm).
[c]Ranked across samples (separately for each size cateogry).
[d]"All" means all structures with widths thinner than 3 μm.
[e]These are the sum of ranks of the Grade 3 samples.
[f]Based on sum of ranks (i.e., a Mann-Whitney test).

Table 4. Tests for significant differences in the relative size distributions of fibers in elustriated dusts from Quebec ore and Grade 3 milled fiber and the magnitude of the corresponding size ratios.

	Primary fibers and bundles only					Total fibers and bundles				
p Value for Mann-Whitney Rank Sum Test[a]										
	L<5	5<L≤10	10<L≤20	20<L≤40	40<L	L<5	5<L≤10	10<L≤20	20<L≤40	40<L
W<0.25	***.05***	***.05***	.10	.10	.20	***.05***	***.05***	.20	.10	.20
0.25≤W<0.4	.35	.10	***.05***	***.05***	***.05***	***.05***	.35	***.05***	***.05***	***.05***
0.4≤W<1.5	.35	.10	.50	***.05***	***.05***	.35	***.05***	.35	***.05***	***.05***
1.5≤W	—	***.05***	.20	.20	.35	—	***.05***	.50	.10	.35
Ratio of Normalized Ratios (fi-G3/fPCME-G3)/(fi-Ore/fPCME-Ore)[b]										
	L<5	5<L≤10	10<L≤20	20<L≤40	40<L	L<5	5<L≤10	10<L≤20	20<L≤40	40<L
W<0.25	***.1***	***2.8***	2.4	2.5	1.1	.1	***2.0***	1.6	2.0	1.3
0.25≤W<0.4	.2	2.0	***4.0***	***3.4***	***5.6***	***.2***	1.4	***2.7***	***3.2***	***5.1***
0.4≤W<1.5	.1	.6	1.0	***3.4***	***1.9***	***.2***	***.6***	1.3	***3.6***	***2.2***
1.5≤W	—	***.2***	.9	1.5	.4	—	***.3***	1.2	2.0	.7

[a]These are *p* values for rank sum tests to determine whether the set of Grade 3 and ore samples are different from one another. The test is applied separately to data for each of the specific size categories defined in the following, bivariate matrix. Bolded-italicized values are significant.
[b]These correspond to the first of the ratio of factors indicated in Equation 11 (and accompanying text) that need to be greater than one to improve agreement in (reconcile) the adjusted lung cancer potency factors (the *KL*'s). Bolded-italicized values correspond with the significant values in the top-half of the table.

Table 5. Comparison of PCM and TEM (PCME) structure loadings on sample filters of Grade 3 milled fiber and Quebec ore dusts generated by elutriation.

	PCM results		TEM ($PCME_{all}$) results[a]			Fraction matrices[b]		
Sample ID	F/mm²	Fibers per filter	F/mm²	Fibers per filter	Percent Abestos[c]	Primary	Total	PCME/PCM[d,e]
Grade 3 Milled Fiber								
1R1	828.0	3.2E+05	819	3.2E+05	100%	3.0%	4.8%	1.0
5R1	1199.6	4.6E+05	1182	4.6E+05	100%	2.4%	3.8%	1.0
Quebec Ore								
34c:	558.5	2.2E+05	179	6.9E+04	80%	26.6%	34.8%	0.3
38c:	496.8	1.9E+05	148	5.7E+04	64%	16.0%	29.3%	0.2
43d:	363.1	1.4E+05	99	3.8E+04	75%	17.6%	26.0%	0.2

[a]In this study, PCME concentrations were determined using a modified ISO Method 10312 Count (see text). Note that PCME has the traditional definition of structures composed of an asbestos mineral. In contrast, PCMEall are all structures exhibiting the appropriate dimensions, no matter the composition.

[b]This is the fraction of the TEM PCME structures that occur as components of matrices (i.e., they are partially embedded in or otherwise associated with nonasbestos material).

[c]This is the fraction of PCMEall structures observed by TEM that are composed of an asbestos mineral.

[d]This is the absolute PCME/PCM ratio observed for the indicated samples, which is determined as Ratio = percent asbestos × PCMEall(f/mm²)/PCM(f/mm²).

[e]Given these data, estimates of the ratio of ratios: (PCME/PCM)G3/(PCME/PCM)Ore range from 3.9 to 5.3. This represents the second of the two factors potentially contributing to the reconciliation of potency factors that are included in Equation 11 (and described in accompanying text).

(Equation 11), if such effects are to explain the differences in potency reported for textile workers and chrysotile miners (see text accompanying Equation 11). The magnitude of the potential adjustments range up to about five (bottom half of Table 4), which could potentially reduce the observed variation in potency between the textile and miner cohorts (a factor of 47) to about 10 (47/5).

As previously indicated, by analyzing the same sample filters by both PCM and TEM in the current study, effects due to differences between PCM and PCME were also evaluated. Table 5 presents a comparison of the paired PCM/TEM analyses. Note that results are only presented for five samples because the sixth sample was lost before this analysis could be completed.

Results presented in Table 5 suggest striking differences between dusts from Grade 3 milled fiber and chrysotile ore. First, although $PCME_{all}$[14] structures from the milled fiber are 100% asbestos, between 20% and 30% of $PCME_{all}$ structures from the ore dust are composed of nonasbestos material. Moreover, up to a third of PCME structures observed in ore dust are at least partially embedded in (or otherwise associated with) nonasbestos particles (i.e., they are part of matrices), whereas fewer than 5% of PCME structures in the Grade 3 dust are similarly associated with nonasbestos particles. Perhaps, most important, although the nature of asbestos structures in the Grade 3 dusts are such that counts by PCM and TEM ($PCME_{all}$) are virtually identical, TEM analysis of ore dust yields $PCME_{all}$ counts that are only about one third that observed by PCM. This suggests that at least some of the particles counted by PCM in the ore dust may not in fact appear fibrous when viewed at the greater magnification and resolving power of the TEM.

The above findings are also consistent with the appearance of the bulk materials themselves. Figure 2 presents optical and SEM photomicrographs of Grade 3 milled fiber and chrysotile ore at 8× and 300×, respectively. Although it is apparent from these photos that Grade 3 material is composed virtually entirely of cotton-like fibers, the ore sample contains both fibers and blocky particles, at least some of which may not be composed of an asbestos mineral. The data presented in Table 5 suggests that dusts from these materials are similarly distinct with Grade 3 dust composed almost exclusively of fibers and ore dust being more complex. These data also suggest at least some of the blocky particles that may be present in the ore dust exhibit dimensions that fall within the definition for PCM structures.

The data in Table 5 can also be used to estimate values for the second of the two factors incorporated into Equation 11 that potentially affect the relationship between potency factors observed, respectively, among textile workers and chrysotile miners. As indicated in Footnote d of the table, the factor representing the "ratio of ratios" for PCME/PCM was observed to range between 3.9 and 5.3. Combined with the values estimated in Table 4 for the first of the two factors (the ratio of ratios for f_i/f_{PCME}), estimates for the product of these two factors range up to a factor of 30, which would reduce the difference between adjusted potency factors, the "$K^*_{L_i}$'s", for the textile and mine cohorts to less than a factor of 2, provided that the factors are linked to the appropriate, long size category. Although this suggests that another piece of the asbestos-risk puzzle has fallen into place (i.e., that the otherwise disparate K_L's for textile manufacturing and chrysotile mining/milling may be entirely reconciled, if exposures are characterized using sufficiently long and thin structures observed by TEM), it must be emphasized that these results are only suggestive. To formally test whether any particular exposure metric adequately reconciles the available epidemiology data will still require a meta-analysis incorporating mortality data from a large and diverse set of exposure environments that are based on data from new analyses suitable for reconstructing the character of the relevant historical exposures (Berman and Crump, 2008b).

[14]Previously defined, see Footnote 10.

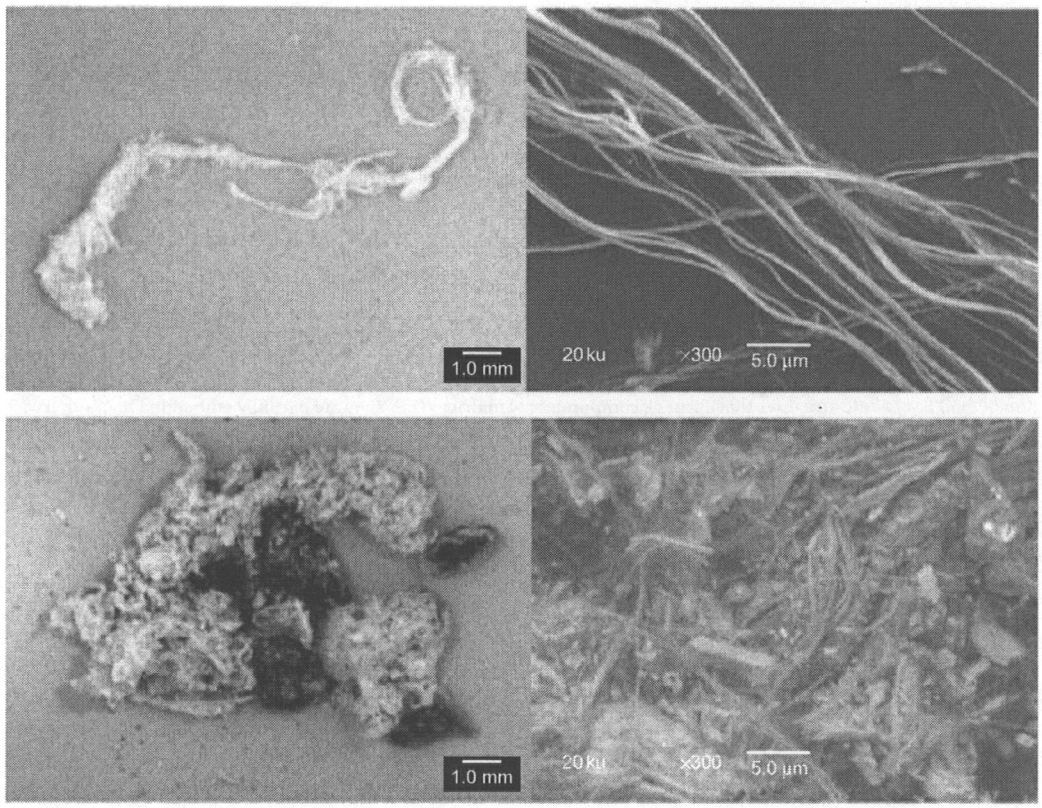


Figure 2. Optical and SEM photomicrographs of Grade 3 milled fiber and raw ore samples. (Upper left) Grade 3 milled fiber; 8×. (Upper right) Grade 3 milled fiber; 300×. (Lower left) Chrysolite ore; 8×. (Lower right) Chrysolite ore; 300×. (Provided by R. J. Lee, Monroeville, PA.)

The above analysis, which was conducted to address the second objective of this study, is based on comparison of dusts generated by elutriation of bulk materials selected to respectively represent the primary feedstock for textile manufacturing and the ore handled by miners/millers. It is recognized, however, that such dusts cannot be considered representative of the corresponding historical exposures, unless it can be shown that the character of dusts generated by elutriation reasonably reproduces the character of dusts generated by commercial processing in the field. Therefore, in the following two sections, dusts generated by elutriation are compared to factory dusts generated during commercial processing that were collected on air filters archived from various, relevant facilities. This is to address the first objective of the current study.

Comparisons between (archived) south carolina textile factory dusts and elurtriated dusts from Grade 3 milled fiber and Quebec ore

Because access to the raw (unsummarized) data from the Dement et al. (2007) study facilitated more formal and substantially more detailed comparison with elutriated dusts than can be conducted with data from other published studies, these data are compared first. Before comparing these factory dusts to the elutriated dusts, however, it is necessary to review the characteristics of each type of dust and the manner in which they were analyzed, so that the most appropriate procedures for comparison can be identified and applied. The characteristics of the elutriated dusts were discussed in the previous section. The characteristics of the factory dusts are reviewed here.

The features of the South Carolina data most relevant to identifying appropriate procedures for comparison are best depicted in Figure 3. Figure 3 is set of bar charts respectively indicating the relative fraction of a specified size category in the size distributions reported for each sample. Each bar of the chart represents the fraction observed in an individual sample. Fractions for each of three size categories are presented in the figure: (a) structures representing PCME; (b) structures longer than, 20 µm; and (c) structures longer than 40 µm with widths between 0.4 and 1.5 µm. In each bar chart, the South Carolina samples are presented in no particular order, except that they are grouped into the 10 processing zones of the factory described by Dement et al. (2007). For later comparison, Groups 11 and 12 in the figure represent, respectively, the (elutriated) Grade 3 and ore samples from Quebec (as noted in the figure).

All of the bar charts in Figure 3 exhibit similar features. Generally, the fraction of structures in each size category varies substantially among samples. Even within most zones of the South Carolina facility, the degree of variation among samples is well over an order of magnitude and contingency-

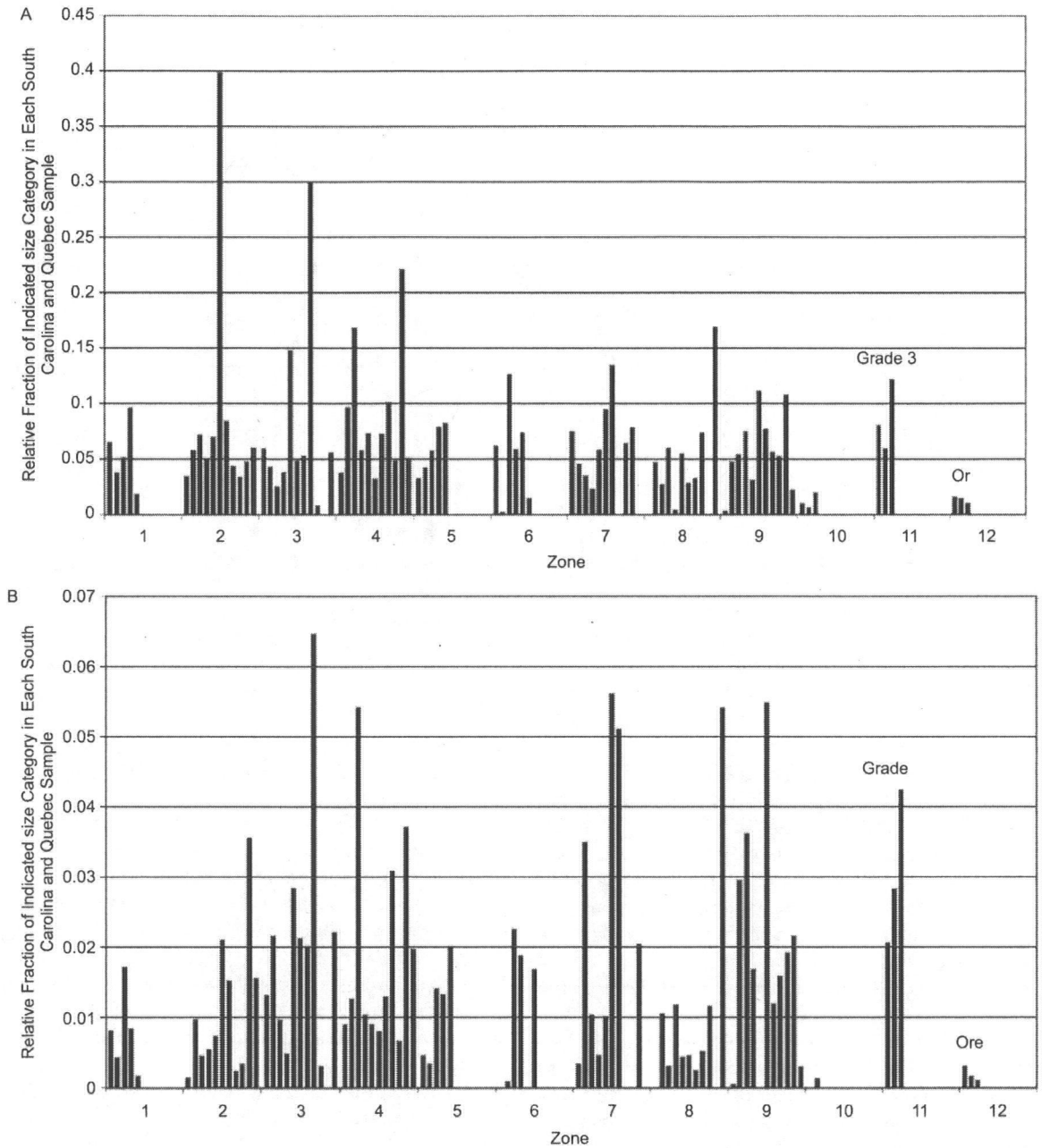


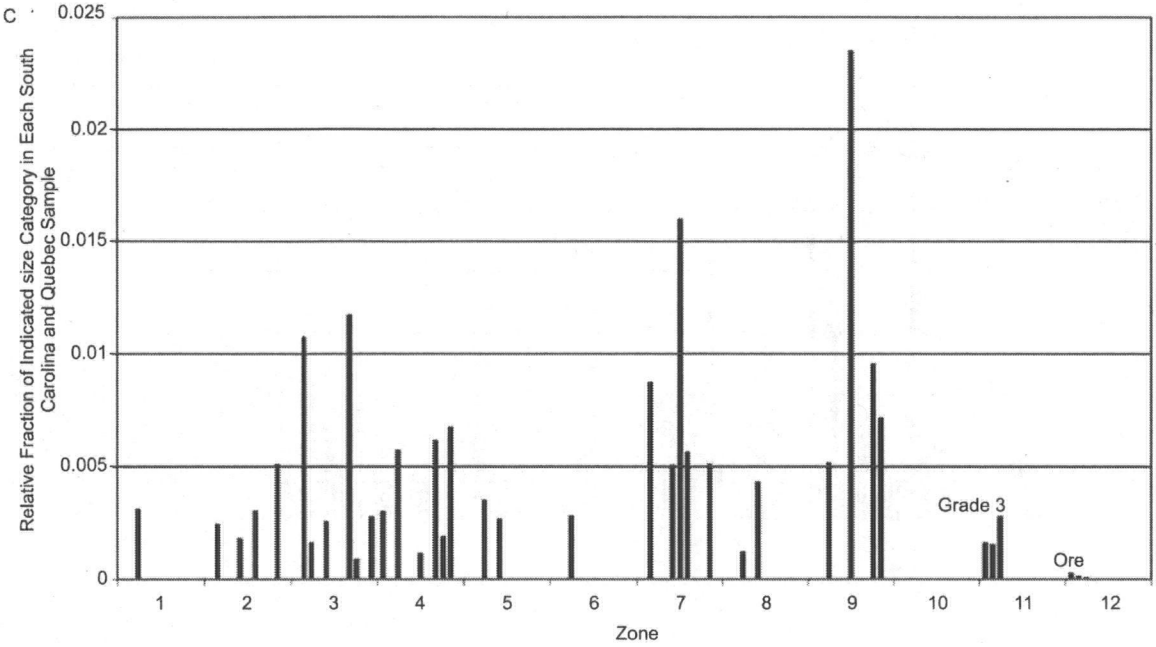
Figure 3. Fraction of (a) PCME structures, (b) structures longer than 20 μm, and (c) structures with L > 40 μm and 0.4 μm < W < 1.5 μm in each (archived sample from the South Carolina textile factory (by zone) compared to (elutriated) Grade 3 and ore samples from Quebec (primary fibers and bundles only).

Figure 3. continued on next page

table analyses confirms that such differences are highly significant (results not shown).

It is also apparent from Figure 3 (by the missing bars in the various images) that, at least for some of the size categories of interest, the South Carolina samples show no detected structures. Of the 83 South Carolina samples depicted in the figure (data for 1 of the 84 samples were lost for this analysis), 3 exhibit no detected PCME structures, 10 exhibit no detected structures longer than 20 μm, and 53 of 83 (64%) exhibit no detected structures longer than 40 μm with widths between 0.4 and 1.5 μm. As described below, the number of samples with no detected structures in specific size categories is an artifact of the manner in which these samples were analyzed. Note that bar charts were also constructed for virtually all of the other size categories of potential interest (identified in Table 1) and the general features of these other bar charts are similar (results not shown).

Figure 3. Continued.



Interestingly, Figure 3 also suggests that the fraction of each size category among (elutriated) Grade 3 samples (depicted on the right) appear to fit reasonably within the middle of the range observed among the South Carolina samples (although to recognize this in Figure 3c, it is important to remember that 64% of the South Carolina samples are missing from the figure as they exhibited no detected structures in the indicated size range). In contrast, the fraction of each size category among (elutriated) ore samples appears generally low, although the fraction in ore samples may parallel the fraction of each size category among Zone 10 samples, which may also be low. This last feature is most apparent for the PCME size category, as all three of the Zone 10 samples exhibit detected concentrations. However, any comparison with Zone 10 samples for the other two structure-size categories must be considered tentative, as only one of the three Zone 10 samples exhibits detected structures longer than 20 µm and none exhibit detected structures that are longer than 40 µm with widths between 0.4 and 1.5 µm.

As previously described (in "Materials and Methods"), there are differences in the protocols used to analyze the (archived) South Carolina factory samples and the (elutriated) Quebec samples. Such differences include that

- short structure counts (length < 5 µm) were determined with substantially greater precision for the South Carolina samples than the Quebec samples and the reverse is true for long structures (40 µm < length);
- differences in the manner in which structure components were counted between the two data sets potentially limits quantitative comparisons to those involving primary structures alone; and
- artifacts potentially introduced due to the interaction between the manner in which category boundaries were defined and the magnifications at which the analyses were conducted introduce additional variation in counts between contiguous size categories in the South Carolina data.

Note that the impact of the first of the above is immediately obvious within the data sets. Although primary structures longer than 40 µm were reported for every elutriated sample (including the ore samples in which such long structures are substantially rarer), due to differences in enumeration, such structures were not detected in almost 40% of the South Carolina samples and more than 60% of the samples show no detection of long structures that are also thin (illustrated in Figure 3c).

An additional factor (not previously discussed) is the variation potentially introduced because the South Carolina and Quebec samples were analyzed by independent microscopists located in different laboratories. A report (Owen Crankshaw, RTI, Research Triangle Park, NC, personal communication, presented at Environmental Information Association Conference in Orlando, FL in 2000) on 5 years of TEM data collected to evaluate the performance of laboratories conducting the AHERA Method (USEPA 1987) indicates that between-laboratory variation associated with several methods exhibit coefficients of variation (CVs) between 0.1 and 1.5 with TEM analyses appearing to represent the higher end of this range; results from the AHERA study itself suggests a CV between 0.3 and 0.6. Similarly, data from an American Society of Testing and Materials (ASTM) study analyzed by Jim Millette (MVA Scientific Consultants, Duluth, GA, personal communication) indicate that TEM

analyses of chrysotile on air filter samples conducted by multiple laboratories exhibit a CV of approximately 0.5.

All of the performance data described in the previous paragraph were generated by comparing results across laboratories performing routine analyses using a common method with which laboratory staff had extensive experience and practice (in many cases including feedback from round-robin studies). For the comparison between South Carolina and Quebec samples in this study, the two laboratories were each conducting analyses using a novel method that was different for each laboratory and with which neither laboratory had much prior experience. Moreover, there was no communication between the two laboratories regarding any of these analyses. In fact, the analyses were conducted years apart with no common knowledge across projects. Given these distinctions, it is safe to assume that the variation introduced by differences between laboratories in this case is substantially greater than that reported above so that, at a minimum, the upper bound of what is reported above likely applies. Correspondingly, this effect potentially contributes additional variability to any comparison between the archived factory dusts and the elutriated dusts.[15]

Given that individual samples within the sample sets of elutriated Grade 3 milled fiber, elutriated ore, and archived factory dusts from South Carolina all exhibit substantial variation that is highly significant (based on contingency table analyses), it is appropriate that Mann-Whitney (rank sum) tests be used to compare across these sets of samples. As previously described, the Mann-Whitney test is sensitive to differences between sample sets that are over and above the variation observed within each sample set. Also, due to differences in the manner that component structures were counted, the comparisons described here are limited to comparisons of primary structures only.

A procedure (described in the following paragraph) was also developed for handling the effects of large numbers of samples with no detected structures in specific size categories (as observed among the South Carolina samples). This was done because, under the conditions that obtain here (where the analytical sensitivities achieved for South Carolina samples exhibiting zero structures lie well within the range of concentrations reported for elutriated samples with detectable structures), the observation of a single structure can radically alter the rank of a particular sample (relative to the rank of a sample exhibiting zero structures).

To address the issue of zeros, the Mann-Whitney tests were applied to each size category in each of two ways. In the first, all samples (including those with zero counts) were included in constructing the ranks, which means that those categories in which a substantial number of South Carolina samples were zero would tend to cause the ranks to be skewed so that South Carolina samples would appear on average to be leaner (have lower concentrations of structures) for the indicated category than is actually the case. A second comparison was also conducted in which South Carolina samples with zero structures in a particular size category were omitted from the analysis. As these tend to be the lowest concentration samples (among the South Carolina samples), removing them tends to skew the ranks such that the South Carolina samples appear on average to be richer (higher in concentrations) for these size categories than is actually the case. Comparing across these two ways for applying the Mann-Whitney test is particularly informative.

Results of applying the Mann-Whitney test to compare size distributions observed respectively in (archived) South Carolina factory dusts and elutriator-generated dusts are presented in Table 6. The top half of the table presents results comparing the combined data set of 83 samples from South Carolina and the three (elutriator-generated) Grade 3 milled fiber samples from Quebec. For reasons previously indicated, the test was applied two ways (both including all 83 South Carolina samples and excluding South Carolina samples with zero detected structures). In all cases, the number of South Carolina samples included in each test is indicated. The test was applied independently to each of, 20 mutually exclusive size categories representing the size distributions for the samples presented. The bottom half of the table also presents results comparing South Carolina samples with elutriated ore samples.

As can be seen in Table 6, although there are multiple size categories that show a significant difference between the South Carolina samples and Grade 3 samples (bolded results), only two categories are significantly different under both of the two conditions evaluated (i.e., with all zeros included and with the zeros excluded). Moreover, with the exception of the single size category for the shortest, thinnest structures, all of the significant differences shown when zeros are included are in the direction in which the South Carolina samples are low (as expected, based on the effects of zeros), whereas all of the significant differences observed when South Carolina samples with zero structures are excluded are high (also as expected).

Among the two size categories that show a significant difference under both of the conditions evaluated, the category containing the longest, thickest structures (40 μm < length and 1.5 μm < width) shows South Carolina samples to contain significantly fewer of these structures (than Grade 3) when zeros are included and significantly more of these structures when zeros are excluded. Both of these results are as expected, based on the effects of the zeros. However, as both these results cannot be simultaneously correct, clearly, this distinction is an artifact associated with the inability to adequately address the large number of nondetects among the South Carolina samples.

The single remaining size category for which a difference between the South Carolina and Grade 3 samples is significant (length < 5 μm and width < 0.25 μm) has the South Carolina sample set being high in both cases. In both cases,

[15]Importantly, because the elutriated Quebec ore and Grade 3 milled fiber samples were analyzed by the same laboratory using a common method, this source of variation was not relevant to comparisons between those analyses, which is why this issue was not previously considered in this paper.

Table 6. Results of Mann-Whitney rank-sum tests comparing specific size categories of structures in dusts on archived filters from the Charleston, SC, textile factory with elutriated dusts generated either from Grade 3 milled fiber or chrysotile ore.

	Size categories (in μm)																			
Length	<5				5–10				10–20				20–40				>40			
Width:	<0.25	0.25–.4	0.4–1.5	>1.5	<0.25	0.25–.4	0.4–1.5	>1.5	<0.25	0.25–.4	0.4–1.5	>1.5	<0.25	0.25–.4	0.4–1.5	>1.5	<0.25	0.25–.4	0.4–1.5	>1.5
Primary SC to Grade 3 (including samples with zero structures)																				
Total number of SC samples	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83
Rank sum for Grade 3 values	194	72	136	—[a]	88	17	185	—[a]	132	16	162	103	90	8	64	59	99	—[b]	94	30
One-tailed *p* value	**.0498**	0.0998	0.4090	—[a]	0.1878	**0.0008**	0.0805	—[a]	0.4434	**0.0006**	0.2005	0.2940	0.2005	**0.00004**	0.0703	0.0524	0.2635	—[b]	0.2275	**0.0060**
Significant?	**(YES)**	NO	NO	—[a]	NO	**YES**	NO	—[a]	NO	**YES**	NO	NO	NO	**YES**	NO	NO	NO	—[b]	NO	**YES**
Relative SC concentrations	**(High)**					**Low**				**Low**				**Low**						**Low**
Primary SC to Grade 3 (excluding samples with zero structures)																				
Total number of SC samples	83	32	58	8	81	15	78	54	77	10	74	50	68	8	62	26	35	4	34	11
Rank sum for Grade 3 values	194	72	136	—[a]	88	17	185	—[a]	132	16	162	103	90	8	64	59	99	—[b]	94	30
One-tailed *p* value	**.0498**	0.0770	**0.0498**	—[a]	0.2005	0.1941	**0.0424**	—[a]	0.3502	0.4956	0.0918	0.1471	0.3502	0.10829	0.1695	0.0736	**0.0012**	—[b]	**0.0030**	**0.0074**
Significant?	**(YES)**	NO	**(YES)**	—[a]	NO	NO	**YES**	—[a]	NO	NO	NO	NO	NO	NO	NO	NO	**YES**	—[b]	**YES**	**YES**
Relative SC concentrations	**(High)**		**High**				**High**										**High**		**High**	**High**
Primary SC to Quebec Ore (including samples with zero structures)																				
Total number of SC samples	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83	83
Rank sum for Grade 3 values	27	—[a]	—[a]	—[a]	220	35	112	103	208	27	162	95	169	18	163	64	98	—[b]	98	—[a]
One-tailed *p* value	**.0043**	—[a]	—[a]	—[a]	**0.0074**	**0.0098**	0.3751		**0.0215**	**0.0043**	0.2005	0.2345	0.1525	**0.00096**	0.1941	0.0703	0.2561	—[b]	0.2561	—[a]
Significant?	**YES**	—[a]	—[a]	—[a]	**YES**	**YES**	NO	NO	**YES**	**YES**	NO	NO	NO	**YES**	NO	NO	NO	—[b]	NO	—[a]
Relative SC concentrations	**Low**				**High**	**Low**			**High**	**Low**				**Low**						
Primary SC to Quebec Ore (excluding samples with zero structures)																				
Total number of SC samples	83	31	57	8	81	15	78	55	77	10	74	50	68	8	62	26	35	4	34	10
Rank sum for Grade 3 values	27	—[a]	—[a]	—[a]	220	35	112	103	208	27	162	95	169	18	163	64	98	—[b]	98	—[a]
One-tailed p value	**.0043**	—[a]	—[a]	—[a]	**0.0038**	0.0639	0.4348	0.2488	**0.0048**	**0.00982**	0.0918	0.2345	**0.02464**	0.1127	**0.00896**	**0.03174**	**0.00164**	—[b]	**0.00039**	—[a]
Significant?	**YES**	—[a]	—[a]	—[a]	**YES**	NO	NO	NO	**YES**	**YES**	NO	NO	**YES**	NO	**YES**	**YES**	**YES**	—[b]	**YES**	—[a]
Relative SC concentrations	**Low**				**High**				**High**	**High**			**High**		**High**	**High**	**High**		**High**	

[a]Too few non-zero ore or Grade 3 samples to support Mann-Whitney Test.
[b]Too few non-zero SC samples to support Mann-Whitney Test.

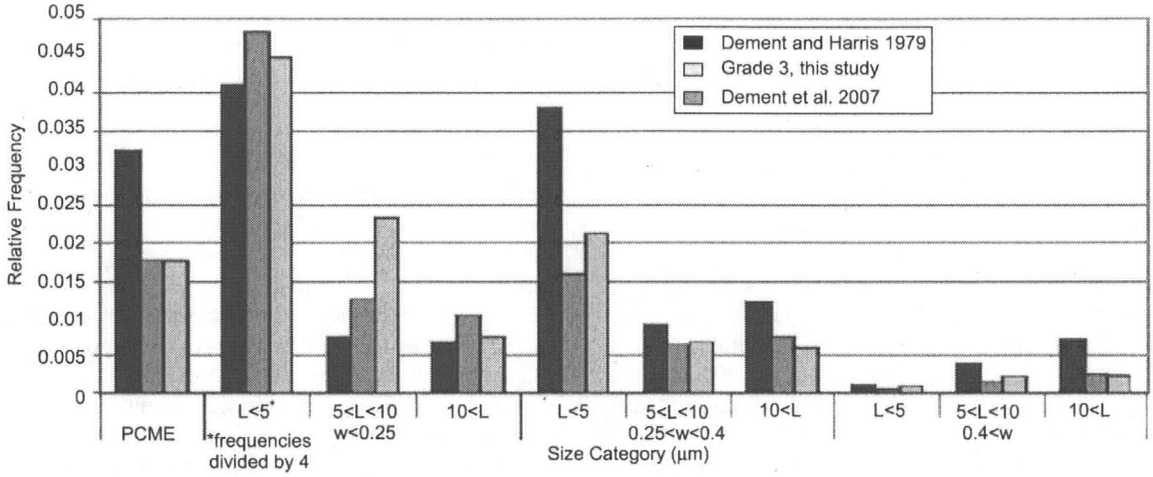


Figure 4. Relative abundance of all fibers and bundles of indicated sizes in textile factory air (South Carolina) and elutriated dust from Grade 3 milled fiber (Quebec).

however, the p value is barely significant (0.498). Moreover, as 20 size categories were independently tested (under each of the two conditions) and the significance level applied was .05, one should expect at least one significant difference to be found (under each condition) simply by chance. Thus, given all of the considerations highlighted above (including especially that the statistical test used to evaluate differences between the two sample sets did not address differences attributable to use of separate laboratories), there is no evidence here to suggest a real difference between the size distributions observed, respectively, among the South Carolina samples of factory dusts and elutriated dusts from Grade 3 samples. At the same time, such results should be considered preliminary and further evaluation is recommended (see Discussion).

A comparison between the South Carolina factory samples and the elutriated ore samples is also presented on the bottom half of Table 6. Although the same considerations apply to these comparisons as those addressed above, a few differences are apparent among this set of Mann-Whitney results. There are now three size categories for which significant differences (in the same direction whether zeros are included or excluded) are observed. Moreover, the p values for two of these pairs of differences (for the size categories: length < 5 and width < 0.25 µm and 5 < length < 10 with width < 0.25 µm) are highly significant ($p < .001$) under both conditions. Thus, based on the direction of the ranks, it does appear that, on the whole, structures in elutriated dusts from ore samples are significantly shorter than those observed at the South Carolina textile factory.

Comparison between other published size distributions in airborne factory dusts and those elutriated from Grade 3 milled fiber or Quebec ore

As previously indicated, because published size distributions represent either results from single analyses or a single distribution derived from pooled data, it is not possible to compare such distributions to the distributions generated in this study using the formal methods previously described. Moreover, such comparisons are limited to the size categories reported in the published distributions, which tend to be more restrictive than the broad range of categories considered heretofore. For example, the size distributions from the South Carolina textile factory that were published in an earlier study (Dement and Harris, 1979) grouped all structures longer than 10 µm into a single length category. Similarly, previously published size distributions generated from dusts in Quebec mines and mills (Gibbs and Hwang, 1980) grouped all structures thicker than 0.3 µm into a single width category. Despite these limitations, however, comparisons between these published distributions and those reported here are informative.

Figure 4 depicts the relative frequencies of the indicated size categories for textile factory air reported by Dement and Harris (1979)[16] and Dement et al. (2007). The corresponding frequencies observed among pooled Grade 3 data generated by elutriation in this study are also presented. Note that to fit all of the size categories at a reasonable scale on the same figure, the relative frequencies for the most abundant category (structures with length < 5 µm and width < 0.25 µm) were divided by a factor of 4 (as noted in the figure).

As can be seen in the Figure 4, agreement across these three distributions is reasonably good as the greatest difference between frequencies within any size category is less than a factor of 3. This compares favorably to the greater than order-of-magnitude differences observed across individual samples in the Dement et al. (2007) study. Moreover, if anything, agreement between the distribution from (elutriated) Grade 3 dust and the distribution reported by Dement et al. (2007) is substantially better than that between the two distributions generated from factory dust: the 1979 and 2007 studies by Dement and coworkers. One

[16]The manner in which the distributions from preparation, twisting, and weaving were combined into a single distribution for this comparison has been previously described (Berman et al., 2008b).

possible explanation for the greater difference between the size distribution from Dement and Harris (1979) and the other two distributions may be that the types of structures counted in 1979 may not have been precisely the same as in the newer studies (because the protocol for counting was different). For example, treatment of component structures may have been different. This cannot be verified, however, because the analytical protocol used in the 1979 study were not described in sufficient detail.

Figure 5 depicts the relative frequencies of the indicated size categories reported for Quebec mine/mill dust (Gibbs and Hwang, 1980) and the elutriated dust generated from bulk ore in this study. Again agreement across these two distributions appears reasonable (although one category shows a difference of about a factor of 4). Importantly, due to lack of documentation, the exact nature of the structures depicted in the published distribution is not known with certainty; they are simply assumed to be total fibers and bundles. However, the details of the analytical protocol (including the counting rules) used in this study are insufficiently documented. Therefore, especially given the limitations and differences in approach, the degree of agreement between the two distributions is reasonably good. Note, as with Figure 4, to fit all of the size categories at a reasonable scale on the same figure, the relative frequencies for the most abundant category (structures with length < 5 μm and width < 0.25 μm) were divided by a factor of 20 (also noted in the figure). Comparing across Figures 4 and 5 (while remembering the adjustments to frequency required to fit each figure), it is clear from all of the distributions considered that textile factory dusts contain substantially greater fractions of long structures than ore dusts.

Evaluating sources of variation in the South Carolina textile factory data

The following analysis was conducted to evaluate the relative degree with which the nature of mechanical processes or the properties of the bulk material to which they are applied determine the characteristics of any resulting dust. This tests a basic principle of the underlying theory supporting use of the elutriator (see Background Section).

Dement et al. (2007) reported that structure size distributions observed in different compartments (zones) of the South Carolina factory vary from one another and they conjectured that this was due to differences in the mechanical processes conducted in each compartment. However, it is also possible that such variation is simply due to natural, temporal variation in the dusts themselves, which (in turn) may be due to natural variation in the type of milled fiber that was used as raw material at the plant. Table 3 illustrates such variation for material from one of the sources of feedstock used at the plant and one would expect that variation in the dusts should exhibit at least as much variation as in the initial feedstocks.

If the mechanical processes associated with each zone played a major role in determining the size characteristics of the dusts generated, one would expect that the samples collected in each zone reflect a common distribution characteristic of that zone. In contrast, if the observed variation (determined for individual size categories as the variance of the relative fraction of that size category across zones, see "Materials and Methods") between zones was instead driven primarily by the temporal variation in the samples, one would expect that grouping the samples by zone would have no unique effect so that the variation observed when grouping the samples by zone would not be any larger than the variation that would otherwise be observed if the samples were grouped arbitrarily.

Results of the simulation conducted to distinguish among these possibilities are presented in Table 7. To minimize the number of samples exhibiting zeros for the size categories evaluated, the relative frequencies were combined across widths within each length category so that only the resulting (mutually exclusive) length categories were evaluated.

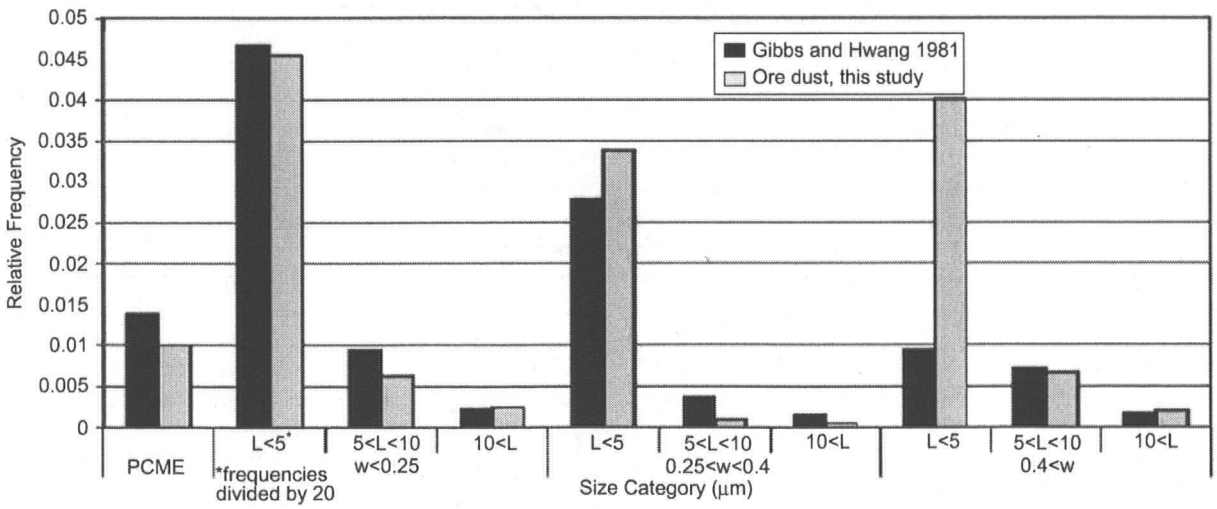


Figure 5. Relative size distribution of all fibers and bundles in air in Quebec mines and mills and elutriated dust from bulk ore samples.

As can be seen in the table, the variation between zones reported by Dement et al. is unremarkable compared to the variation observed by randomly regrouping the samples. In all cases except that for lengths between 20 and 40 μm, the variation observed by these authors falls within the 25th and 75th percentiles of the range of variation observed across random groupings. Even for the category with lengths between 20 and 40 μm, the variation across the groupings in the original zones falls between the 15th and 85th percentiles of the distribution obtained by randomly grouping the samples. Among other things, this suggests that the differences observed between zones at the South Carolina factory are driven primarily by differences in the times that samples were collected from each zone (which would reflect differences in the temporal variation in feedstocks) rather than anything about the particular activities that occur within the zones themselves (although smaller effects that my be zone-specific cannot be ruled out). Such a finding is further reinforced from impressions gained from viewing Figure 3. It is clear from this figure that the degree of variation observed between samples (even within zones) is substantially greater than any potential difference between the zones themselves.

Discussion

The major findings of this study are that

1. textile workers were exposed to substantially longer asbestos structures than chrysotile miners and millers;
2. PCM-counted structures in textile factory dusts were virtually 100% asbestos and 100% asbestiform. In contrast, at least two thirds of the structures counted by PCM in chrysotile mine and mill dusts were either blocky and irregular (so that they were not counted as $PCME_{all}$ structures by TEM) or were not composed of an asbestos mineral;
3. taken together, the above-listed differences in the character of the exposures respectively experienced by textile workers and chrysotile miners/millers can potentially explain the difference in lung cancer potency observed between these cohorts;
4. differences in size distributions observed in dusts from different zones of the South Carolina textile factory are driven primarily (although perhaps not exclusively) by temporal variation in the Grade 3 milled fiber handled at the plant, rather than differences in the mechanical operations conducted in each zone of the plant; and
5. most importantly, elutriator-generated size distributions from appropriately selected bulk materials mimic those directly determined from factory dusts with sufficient reliability to support comparisons between historical exposures experienced by the various cohorts studied by epidemiologists.

The implications of each of these findings are addressed below along with a discussion of the bigger picture associated with asbestos risk assessment and corresponding requirements for analysis.

Finding 1

Textile workers were exposed to substantially longer asbestos structures than chrysotile miners and millers.

The first of the above findings is based on comparisons among the elutriator-generated dusts analyzed in this study (Tables 1, 4, 5; Figure 1), among size distributions determined in factory dusts reported in several studies (Figures 4, 5; Dement and Harris, 1979; Gibbs and Hwang, 1975, 1980; compared in Berman and Crump, 2003, 2008b), and between elutriator-generated and factory-derived dusts (Table 6; Figure 3).

Findings from a reevaluation of data from relevant lung-tissue studies (Sebastien et al., 1989; Case et al., 2000) are also consistent with the above findings (Berman and Crump, 2003). Given their particular relevance, these findings are described in detail below.

Although Sebastien et al. (1989) initially reported that size distributions in lungs samples from South Carolina and Quebec cohort members are not different, these authors failed to account for differences in degradation and clearance before making their comparison. Focusing on those portions of the size distributions reported by Sebastien et al. that are least likely to be affected by degradation and clearance produces very different results.

The Sebastien et al. data were reevaluated considering only chrysotile and tremolite structures longer than 20 μm. This is because, based on animal studies of retention, degradation, and clearance (as reviewed and reconciled in

Table 7. Comparison in the variation of fiber size distributions among simulated and actual zones at the South Carolina textile factory (by length)[a]

	Size Categories (μm)				
Percentile	L<5	5<L<10	10<L<20	20<L<40	40<L
5th percentile	5.1E-03	1.6E-03	4.4E-04	1.0E-04	4.4E-05
25th percentile	8.9E-03	2.8E-03	7.6E-04	1.9E-04	8.6E-05
50th percentile	1.2E-02	3.9E-03	1.1E-03	2.9E-04	1.3E-04
75th percentile	1.7E-02	5.0E-03	1.5E-03	4.4E-04	1.9E-04
95th percentile	2.4E-02	6.8E-03	2.4E-03	8.5E-04	4.1E-04
South Carolina Data	**1.7E-02**	**4.6E-03**	**1.5E-03**	**6.0E-04**	**2.1E-04**
Approximate Percentile	0.75	0.65	0.7	0.85	0.75
Number of zeros	0	0	0	2	4

[a]Based on the data described in Dement et al. (2007), which was graciously provided by Everett Lehman of NIOSH. The data depicted in the table are the variances in the relative fraction of the indicated size category across the 10 zones of the factory.

Table 8. Estimated concentrations of sized fibers observed in the lungs of Thetford miners and South Carolina textile workers[a]

	Mean lung concentration[b]				Number of fibers		
Fiber type	Thetford	South Carolina	Units	Ratio: Th/SC	Thetford	South Carolina	Size range of fibers
Chrys	5.3	0.63	f/μg lung	8.4	371	226	Length > 5 μm
Trem	18.4	0.38	f/μg lung	48.4	405	175	
Chrys	1.73	0.17	f/μg lung	10.0	121	62	Length > 8 μm
Trem	3.9	0.091	f/μg lung	43.0	86	42	
Chrys	0.59	0.07	f/μg lung	8.4	41	25	Length > 13 μm
Trem	0.72	0.024	f/μg lung	30.5	16	11	
Chrys	0.16	0.031	f/μg lung	5.2	11	11	Length > 20 μm
Trem	0.037	0.008	f/μg lung	4.4	1	4	

[a]Derived from data presented in Tables 4 and 5 of Sebastien et al. (1989).
[b]Geometric mean.

Berman and Crump, 2003, Section 6.2), structures longer than approximately 20 μm are cleared only slowly from the lungs, as long as their in vivo solubilities are sufficiently limited (Bellman et al., 1986, 1987; Bernstein et al., 1996; Coin et al., 1992, 1994; Eastes and Hadley, 1995; Hesterberg et al., 1993, 1995, 1996, 1997, 1998a, 1998b; Kauffer et al., 1987; Morgan et al., 1978, 1980; Morgan and Holmes, 1980; Oberdorster et al., 1988; Roggli and Brody, 1984; Roggli et al., 1987; Wright and Kushner, 1975). Moreover, although both tremolite (as all other amphiboles) and chrysotile are sufficiently insoluble (Hume and Rimstidt, 1992; Zoitus et al., 1997) to preclude rapid clearance of structures longer than 20 μm, long chrysotile structures (being more soluble than amphiboles) exhibit limited clearance by dissolution while tremolite structures are likely biopersistent (Bellman et al., 1986, 1987; Hesterberg, 1998b; Warheit et al., 1997). These general features of the fate of tremolite (and other amphibole) structures and chrysotile in vivo were also generally recapitulated in findings from various human pathology studies of lung-fiber content and physiological-kinetic models developed to address retention, degradation, and clearance (Albin et al., 1994; Churg et al., 1984; Finkelstein and Dufresne, 1999; McDonald et al., 1993; Pooley, 1976; Timbrell, 1982; Eastes and Hadley, 1994, 1996; Stober et al., 1993; Yu and Asgharian, 1990; Yu et al., 1990, 1991). However, lack of explicit focus on structures longer than 20 μm and other methodological limitations in some of these studies limited the comparability of their results (reviewed and reconciled in Berman and Crump, 2003).

Table 8 presents the estimated, relative concentrations of specific lengths of structures observed in lung tissue among Thetford Miners[17] and South Carolina textile workers, respectively (source: Sebastien et al., 1989). The estimated concentrations presented in columns 2 and 3 of this table were derived as follows. For the first length category (length > 5 μm), concentrations are taken directly from Table 5 of Sebastien et al. (1989) (the geometric means are presented). Concentrations for the remaining length categories were estimated by multiplying the concentrations for this first length category by the fraction of the size distribution represented by each succeeding length category (as provided in Table 4 of Sebastien et al.). So that the relative precision of these concentration estimates can be evaluated, an estimate of the numbers of structures included in each length category (from the total used to derive the size distribution in Table 4 of Sebastien et al.) is also provided.

It is instructive to compare the ratios of lung tissue concentrations presented in Table 8 to the Thetford:South Carolina ratios of mean cumulative exposures for chrysotile and tremolite among the cohort members included in the Sebastien et al. (1989) study. A rough estimate of cumulative exposure for each set of workers can be derived as the product of the mean duration of exposure and the mean intensity of exposure. Thus, for example, mean cumulative exposure in Thetford was 32.6 years × 19.5 mpcf or 635.7 mpcfy (millions of particles per cubic foot-years). Similarly, for South Carolina, mean cumulative exposure was 25.65 mpcfy, which gives a Thetford/South Carolina ratio of 24.8. This presumably represents the relative cumulative exposure to chrysotile. For tremolite, Sebastien and coworkers report that, based on a regression analysis, the fraction of tremolite structures among total asbestos structures were likely only 0.4 times as much in South Carolina as in Thetford (where they likely averaged 1% of total structures).[18] Therefore, the ratio of cumulative exposures to tremolite for the sets of cohort members studied by Sebastien and coworkers is likely 62.

As indicated in Table 8, for chrysotile, the ratio of lung structure concentrations remains approximately constant at about 9 (varying only between 8.4 and 10) for all of the size ranges reported except the longest. For the longest category (length > 20), however, the ratio drops to 5. Because structures longer than 20 μm are expected to be the most persistent in the body (see review in Berman and Crump, 2003, Section 6.2), it may be that the ratio of 5 best represents the relative concentrations of long chrysotile structures among the two sets of cohort members.

[17] Thetford Mines is a mining area in Quebec from which a substantial fraction of the Quebec cohort of miners/millers derives.

[18]Interestingly, three of the structures observed among the approximately, 2000 structures counted across the three elutriated Grade 3 milled fiber samples analyzed for this study were found to be tremolite. No tremolite fibers were observed among ore samples. For the reasons previously cited in the Background section, however, a substantially greater number of samples would need to be analyzed before any meaningful inferences might be drawn from such data.

Table 9. Estimated mean airborne exposure concentrations and associated lung-fiber contents for a selected set of textile workers, miners, and Millers[a,b]

Location	Mean airborne exposure concentration (mpcfy)	Lung chrysotile content (long fibers) (f/μg)	Lung tremolite content (long fibers) (f/μg)	Lung total amphibole content (long fibers) (f/μg)
Quebec Mining	186	0.231	0.325	0.349
SC Textiles	3.63	0.054	0.027	0.0064
Ratio	51.24	4.28	12.04	5.45

[a]Derived from data presented in Table 2 of Case et al. (2000).

Because this ratio (for the long structures found in the lung) is only approximately one fifth of the estimated ratio for the cumulative exposure to chrysotile (24.8), this suggests that the South Carolina cohort may indeed have been exposed to dusts enriched in long structures relative to dusts experienced at Thetford. Because the estimate of this ratio is based on counts of at least 11 structures from Thetford and South Carolina, respectively, it is unlikely that this ratio will vary by more than a factor of 2 or 3 (the 95% CI around 11 structures, based on a Poisson distribution, is 6–19).

The trend with tremolite is even more striking. Moreover, as previously indicated, because tremolite structures are biodurable, it is the tremolite structures longer than 20 μm that may best represent the ratio of long structures in general to which these two groups of cohort members were exposed; tremolite may serve as a surrogate for earlier chrysotile lung content that may itself have decreased over time. The ratios observed among tremolite structures steadily decrease from approximately 50 for structures longer than 5 μm to 4.4 for structures longer than 20 μm, although this last value is uncertain (due to it being based on only one structure observed among Thetford-derived lungs and only four structures among South Carolina-derived lungs). In fact, these data are statistically consistent even with a ratio considerably less than 1 (i.e., with a considerably higher concentration of long tremolite structures in South Carolina than in Quebec). Given that the ratio of the original cumulative exposures for tremolite was estimated to be 62, that the ratio of long tremolite structures is only 4.4 suggests that dusts in South Carolina may have been highly enriched in long structures (of all types).

Case et al. (2000) demonstrates even more strongly that South Carolina textile workers were exposed to structures that were substantially longer than those inhaled by Quebec miners and millers. In this study, lung structures contents were determined for 64 deceased textile workers and 43 deceased chrysotile miners and millers, respectively, which represent randomly selected subsets of the workers, miners, and millers for whom lung-fiber content was previously described by Sebastien et al. (1989), discussed above. Case et al. focused specifically on the counting of structures longer than 18 μm.

Results from the Case et al. (2000) study are summarized in Table 9. As indicated in Table 9, the mean cumulative exposure to which the selected cohort members from Quebec and South Carolina were exposed in this study was 186 and 3.63 mpcfy, respectively. This gives a Quebec/South Carolina ratio of approximately 50. In contrast, the Quebec/South Carolina ratios of the concentrations of asbestos structures observed in lungs among these selected cohort members are substantially smaller (4 for long chrysotile, 12 for long tremolite, and 5 for long amphibole). This implies that the lungs of South Carolina workers are substantially enriched in these long structures relative to the lungs of Quebec miners and millers. Moreover, because substantial numbers of long structures were counted in these analyses, the uncertainty of these ratios is relatively small.

Importantly, Case et al. indicated in their paper that because they observed substantially greater absolute numbers of long structures in the lungs of Quebec miners than in the lungs of South Carolina workers, they concluded that (regardless of the above analysis) Quebec miners were still exposed to a greater absolute number of long structures than South Carolina workers. However, this does not appear to be a valid conclusion for the reasons described in the following two paragraphs.

Before comparing absolute lung concentrations between Quebec miners and South Carolina textile workers, it is necessary to adjust the mean concentrations observed by Case et al. (2000) to account for the differences between the mean exposures experienced by the set of workers from which lung samples were obtained and the mean exposures experienced, respectively, by each entire cohort. Estimates of the mean exposures for each entire cohort can be derived from Table B-1 of Berman and Crump (2008a) for Quebec miners and Table B-6 of Berman and Crump for South Carolina textile workers. Assuming that the number of expected cancers for subgroups are approximately proportional to the number of cohort members estimated for each of the subgroups listed in the tables,[19] an estimate of the geometric mean exposure (in millions of particle per cubic foot-years or mpcfy) experienced by each cohort is derived by

1. taking the natural log of the mean exposure indicated for each exposure subgroup in the table;
2. multiplying this value by the expected number of cancers for the corresponding subgroup;
3. summing over all subgroups;
4. dividing by the total number of expected cancers; and
5. taking the exponential of the quotient.

By applying the above, it is estimated that the geometric mean exposure experienced by miners/millers in the Quebec cohort is approximately 45 mpcfy, whereas for South Carolina textile workers it is 8.1 mpcfy.

[19]As long as the age distributions across the subgroups are not radically different, this assumption is reasonable.

Given the above results, the mean lung concentrations experienced by each cohort would be approximated by multiplying the concentrations reported in Table 2 of Case et al. (2000) by the ratio of the mean exposure for the entire cohort to the mean exposure for the subset of workers from whom lung tissue samples were analyzed. For miners and millers, this ratio is 0.24 (45/186) and for textile workers, the ratio is 2.2 (8.1/3.6). Adjusting the values in Table 2 from Case et al. accordingly, the absolute concentrations of long chrysotile fibers and long total amphibole fibers in the lungs of textile workers are higher than miners/millers, whereas for long tremolite, lung concentrations are nearly equal (results not shown). Although these are only crude estimates that should be more properly evaluated using the raw data, it is apparent that Case et al. overlooked the need to normalize absolute lung concentrations to reflect the experiences of each entire cohort before concluding that miners/millers were exposed to larger absolute numbers of long structures. Following discussion of this issue and pending further analysis of the raw data, Case now agrees with this finding. Bruce Case, personal communication.

Finding 2

PCM-counted structures in textile factory dusts were virtually 100% asbestos and 100% asbestiform. In contrast, at least two thirds of the structures counted by PCM in chrysotile mine and mill dusts were either blocky and irregular (so that they were not counted as PCMEall structures by TEM) or were not composed of an asbestos mineral.

Regarding the second of the above-listed findings, this appears to be the first study in which the character of PCM and PCME counts are explicitly compared across exposures experienced by cohorts from different environments. Results in Table 5 suggest a need to conduct counts by TEM, as opposed to PCM, both to eliminate structures not composed of asbestos minerals and to better discriminate among the morphological types that need to be counted. As indicated in Table 5 (and accompanying discussion), when viewed using TEM or PCM, there are differences in the structures that are considered countable. This also suggests that the character of dusts retain properties similar to those exhibited by the bulk materials from which they are generated (Figure 2); whereas dusts from Grade 3 are almost exclusively fibers and bundles that are all asbestos, dusts from ore also appear to contain blocky particles that may satisfy the dimensional requirements to be counted by PCM, yet not all of these particles are composed of an asbestos mineral or are considered countable when viewed by TEM. Such findings are consistent with the findings of Wylie and Bailey (1992).

Finding 3

Taken together, the above-listed differences in the character of the exposures respectively experienced by textile workers and chrysotile miners/millers can potentially explain the difference in lung cancer potency observed between these cohorts.

Regarding the third finding listed above, after accounting for differences within sample types, results in Table 4 suggest that longer and thinner structures compared to PCM (i.e., at least as long as, 20 μm and no thicker than 1.5 μm) need to be separately enumerated to adequately reconcile the difference in lung potencies observed respectively among miners and textile workers. It may even be necessary to separately enumerate structures as thin as 0.4 μm, as these thinner structures (among the longer structures) appear to even better reconcile the difference between lung potencies than the thicker ones; they exhibit among the largest ratios in the table. Such suggestions are consistent with inferences from both animal inhalation studies (Berman et al., 1995) and human pathology studies (see Finding 1 above).

When the effects of size (described in Table 4 and the previous paragraph) are addressed along with differences between PCM and PCME counts (described in Table 5 and Finding 2 above), the difference in lung potency estimates observed respectively among textile workers and chrysotile miners can potentially be entirely reconciled; the product of the largest of the adjustment factors respectively indicated in each of Tables 4 and 5 is approximately 30 and if this is substituted into Equation 11, it would reduce the differences in lung potency estimates for these two cohorts to less than a factor of 2. However, whether an exposure metric incorporating only structures longer than 20 μm that are also thin (potentially thinner than 0.4 μm) and that are analyzed by TEM will similarly reconcile potency estimates from the broader epidemiological literature remains to be determined; evaluating such hypotheses would require completing a robust meta-analysis addressing a substantial number of the diverse environments that have been studied by epidemiologists. The study would also need to incorporate improved reconstructions of the character of historical exposures experienced by the relevant cohorts.

Finding 4

Differences in size distributions observed in dusts from different zones of the South Carolina textile factory are driven primarily (although perhaps not exclusively) by temporal variation in the Grade 3 milled fiber handled at the plant, rather than differences in the mechanical operations conducted in each zone of the plant.

Regarding the fourth of the above-listed findings, results of the contingency-table analyses in Table 2 indicate that samples of Grade 3 (or ore) that were processed or mined at different times produce laboratory-generated dusts that significantly differ from one another in character. This is consistent with the significant differences also observed among samples from the South Carolina textile factory studied by Dement et al. (2007), even among samples collected from within the same zone of the factory (Figure 3).

Results in Figure 3 and especially Table 7 indicate that the variation in the character of dusts observed between zones at the South Carolina factory is primarily associated with temporal variation in the dusts themselves, rather than to differences potentially introduced by the specific mechanical processing conducted in the different zones. Given the likelihood that variation in the dusts are in turn driven by

the temporal variation in the Grade 3 feedstock primarily used at the factory, these results indicate that it is primarily the properties of the material processed that mediates the character of dusts generated at a factory, rather than the nature of the mechanical manipulation to which a bulk material is subjected.

At the same time, the degree of agreement observed between the elutriated Grade 3 dusts and the dusts from the South Carolina Factory (Table 6) is particularly remarkable considering that not all of the feedstock used at the South Carolina textile factory came from the same mine as the Grade 3 samples and there is little overlap in the time period covered by the Grade 3 and factory dust samples. Thus, the similarity of the field- and laboratory-generated dusts observed in this study is consistent both with

1. the theory that the properties of the bulk material processed (in both the field and the laboratory) are the primary determinants of the character of the dusts generated (in both locales); and
2. despite substantial spatial variation in deposits (which also translates into substantial temporal variation among mine products), several prominent properties distinguish the ore from milled products generally.

All of these findings are consistent with the literature previously cited (Turcotte, 1986; Wylie, 1993; Wylie and Schweitzer, 1982) in the Background section.

It should also be noted that as all previously published epidemiology studies such as (listed in Table 10) express exposure as PCM (or cruder measurements), which simply represent number concentrations of a fixed size-range of structures with no information on sizes or types, and previously published studies of size distributions present only a single distribution from either a single sample or pooled data (reviewed in Berman and Crump, 2003, 2008b), Dement et al. (2007) and this study are the first to provide information on the spatial and temporal variation in the character of exposure within environments of epidemiological interest.

Finding 5

Elutriator-generated size distributions from appropriately selected bulk materials mimic those directly determined from factory dusts with sufficient reliability to support comparisons between historical exposures experienced by the various cohorts studied by epidemiologists.

It is clear from the results of this study (Table 6 and accompanying text) that the sources of the differences in size distributions observed between the South Carolina samples of factory dusts and the (elutriated) Grade 3 samples can be largely (if not completely) explained by differences in the analytical protocols applied to each sample set or from lack of control for the substantial (natural) variation in the bulk materials contributing to these dusts and, correspondingly, the temporal variation in the South Carolina dusts themselves. It also appears that any such differences are sufficiently small to support reasonable use of elutriator-generated dusts to explore the larger differences in dusts that occur between environments. Nevertheless, further study of these issues is warranted to better define the confidence that can be placed in use of elutriator-generated dusts to represent the character of historical exposures. In fact, given both the observations described above and the theoretical considerations described in the Background section (and summarized under "Finding 4"), it is likely that more formal tests of the elutriator (in which the extraneous factors identified above are rigidly controlled and separately considered) would only show greater correspondence.

Several improvements to the current study are envisioned. Regarding the comparison between elutriated dusts from Grade 3 milled fiber and South Carolina factory dusts, differences between analytical protocols can be eliminated by reanalyzing grids from a selected subset of South Carolina samples using the protocol and laboratory employed originally to analyze the Grade 3 samples. The reverse (having the Grade 3 samples reanalyzed using the protocol and laboratory employed originally to analyze the South Carolina samples) would also be useful (especially as an independent check). However, expanding use of the protocol originally applied to the Grade 3 samples would facilitate testing of a broader range of hypotheses by assuring that a sufficient number of longer structures are observed in all of the individual samples. Additional samples of Grade 3 milled fiber should also be analyzed at the same time. This would improve the overall power to distinguish among the two groups of samples. Moreover, by including Grade 3 samples generated over a larger range of time and (perhaps) additional mines, the natural variation in these materials (across time and space) could simultaneously be better characterized. Similarly, analyzing additional (equally diverse) ore samples would provide a better understanding of the natural variation in ore across time and mines.

Importantly, although the above-envisioned supplements to the current study would improve the ability to compare field- and laboratory-generated dusts (by controlling for the effects of analytical protocol and use of different laboratories) and provide a better understanding of the contributions from natural variation, they would still not allow for full control of the effects of natural variation. One way to accomplish the latter would be to visit a small number of active mineral processing facilities to allow selection of one or more process operations from which samples can be collected of both the bulk material being processed (and/or the bulk product from the operation) and the dust generated from the operation *at the same time that the bulk material that was sampled is processed.* Only by comparing the character of dusts generated in the field during processing of the very same bulk material that is elutriated in the laboratory will it be possible to fully distinguish between any unique effects of the elutriator and effects attributable to natural spatial/temporal variation.

As there are no active asbestos mines left in the United States, such a study would either need to be conducted

Table 10. Most recent updates published for epidemiology studies of cancer mortality in asbestos-related environments.

Fiber type/Location	Epidemiological references (most recent update only)	Nature of cohort and study environment
Primarily Asbestiform Amphibole		
Whitenoom, Australia	Berry et al. (2004)	Crocidolite (amphibole asbestos) miners and millers
Patterson, NJ factory	Seidman (1986)	Amphibole asbestos insulation manufaturers
Tyler, Texas factory	Levin et al. (1998)	Amphibole asbestos insulation manufaturers
Gas mask Factory	McDonald et al. (2006)	Gas mask manufacturers using milled crocidolite (amphibole asbestos) fiber
Mixed Asbestiform and Nonasbestiform Amphibole		
Libby, Montana	Sullivan (2007)	Vermiculite miners exposed to asbestiform and nonasbestiform amphibole asbestos
	McDonald et al. (2004)	Vermiculite miners exposed to asbestiform and nonasbestiform amphibole asbestos
Primarily Nonasbestiform Amphibole		
Homestake, SD	Steenland et al. (1995)	Gold miners exposed to nonasbestiform amphiboles
Taconite Mines, MN	University of Minnesota study in progress (MPH 2007)	Taconite miners and millers exposed to nonasbestiform amphiboles
Vanderbilt Talc, NY	Honda et al. (2002)	Talc miners exposed to mixed amphiboles
Mixed Asbestiform Amphibole and Chrysotile Dusts		
British factory	Berry and Newhouse (1983)	Friction product manufacturers exposed to mixed asbestos milled fiber
Ontario factory	Finkelstein (1984)	Asbestos-cement manufacturers exposed to mixed asbestos milled fiber
New Orleans plants	Hughes et al. (1987)	Asbestos-cement manufacturers exposed to mixed asbestos milled fiber
Swedish plant	Albin et al. (1990)	Asbestos-cement manufacturers exposed to mixed asbestos milled fiber
Belgium factory	Laquet et al. (1980)	Asbestos-cement manufacturers exposed to mixed asbestos milled fiber
US retirees	Enterline et al. (1986)	Manufacturers of miscellaneous asbestos products exposed to mixed asbestos milled fiber
Asbestos, Quebec	Liddell et al. (1997)	Manufacturers of miscellaneous asbestos products exposed to mixed asbestos milled fiber
US insulation workers	Selikoff and Seidman (1991)	Mixed asbestos insulation applicators exposed to dusts from insulation products containing asbestos
Pennsylvania plant	McDonald et al. (1983b)	Mixed asbestos textile manufactors exposed to textile-grade milled asbestos fiber
Rochdale, England plant	Peto (1985)	
Predominantly Chrysotile (Potentially with Varied, Minor Amounts of Amphibole)		
Quebec mines and mills	Liddell et al. (1997)	Chrysotile miners and millers
Italian mine and mill	Piolatto et al. (1990)	Chrysotile miners and millers
Connecticut plant	McDonald et al. (1983a)	Friction product manufacturers exposed to predominantly milled chrysotile fiber
New Orleans plants	Hughes et al. (1987)	Asbestos-cement pipe manufacturers exposed predominantly to milled chrysotile fiber
South Carolina plant	Hein et al. (2006)	Asbestos-textile manufacturers exposed to predominantly milled chrysotile fiber
	McDonald et al. (1984)	Asbestos-textile manufacturers exposed to predominantly milled chrysotile fiber
North Carolina plant	Loomis et al. (2007)	Asbestos-textile manufacturers exposed to predominantly milled chrysotile fiber
Chinese Factory	Yano et al. (2001)	Manufacturers of miscellaneous asbestos products exposed to predominantly milled chrysotile fiber

internationally or would need to be conducted on nonasbestos materials. Nevertheless, as long as the size distributions of particles were adequately characterized, conducting such a study on nonasbestos minerals would be informative. Moreover, combining this latter study with the expanded comparison of Grade 3 dusts and South Carolina dusts (described above) would allow the effects of the remaining factors confounding comparison between factory- and elutriator-generated dusts to be distinguished.

The bigger picture

Understanding the effects of structure size and type on potency is of more than academic interest. Although asbestos is no longer mined in the United States and its use in commerce has been all but eliminated, substantial quantities of asbestos-containing products remain in place in both commercial establishments and residences. More importantly, asbestos occurs naturally in rocks and soils throughout the nation so that exposure to asbestos may result from any excavation or construction, agricultural tilling, quarrying, or mining (of any products) that occur in such locations. In fact, one of the two main mineral groups known to form asbestos (amphibole) makes up about 5% of the earth's crust (Klein, 1993). Although the vast majority of such deposits are composed of crystalline forms (habits) not considered to be asbestos (Klein, 1993; Veblen and Wylie, 1993; Siegrist and Wylie, 1980; Wylie et al., 1993), when disturbed, such minerals may generate cleavage fragments, which are elongated particles that, depending on the dimensions included in counts of asbestos structures, may contribute to the count (Virta et al. 1983). Moreover, the precise boundary between the size and habit of particles that contribute to asbestos-related disease has not been definitively determined and these factors will need to be delineated to permit quantitative assessment of asbestos-related cancer risks across the environments of general

interest (ERG 2003; Berman and Crump, 2003, 2008a, 2008b).

Given the above, there is a compelling need to develop quantitative models for predicting asbestos-related cancer risk that can be applied with confidence across (unstudied) environments of interest. To assure that adequate confidence can be placed in these models, however, it would first be necessary to demonstrate that such models can adequately predict asbestos-related risk in the available (studied) environments. As previously indicated (see "Background"), however, cancer potency estimates vary substantially across the studied environments, and although much evidence (including results from this study) indicates that such variation can potentially be explained by the effects of structure size, type, and (perhaps) habit, models incorporating these effects have yet to completely reconcile the observed differences.

It is not lack of a rich database of diverse epidemiology studies that has so far prevented development of a model that adequately reconciles these studies. As indicated in Table 10, the literature currently contains at least 27 separate mortality studies potentially suitable for supporting development of a risk model. Note that the table in fact includes only those studies reporting the most recent follow-up in each environment from each research team, so that the number of studies is actually even larger. This database covers 25 separate environments that encompass a broad range in both the intensity and character (sizes and types of asbestos structures) of exposures (Table 10). The data set also includes environments in which the relevant exposures were composed primarily of the nonasbestiform varieties of amphiboles (Berman and Crump, 2008b).

Rather, it is the lack of adequate quantification of the character of the exposures across the environments listed in Table 10 that has heretofore hindered the development of an adequate risk model for asbestos. Thus, if some combination of the four potential sources of information useful for determining the character of exposure that were described in the Background section are applied to a sufficient number of the studies in Table 10, it should be possible to generate the data required to develop comprehensive risk models (one for each disease end point) that could be applied in all environments.

Given the inadequacy of the published data, the limited availability of archived filters, and limitations associated with use of lung tissue samples (as previously described), the elutriator may have an important role to play in the effort to reconstruct the character of historical exposures. Thus, although results from this study indicate that the elutriator is suitable for such a purpose, further determination of the confidence that can be placed in the fidelity of elutriated dusts is also warranted.

Summary and conclusions

Results of a recent meta-analysis indicate that the variation in potency factors observed across published epidemiology studies can be substantially reconciled (especially for mesothelioma) by considering the effects of fiber size and mineral type, but that better characterization of the relevant, historical exposures is needed before improved exposure metrics that are potentially capable of fully reconciling the disparate potency factors can be evaluated. Thus, the relative merits of traditional approaches for better characterizing historical exposures were compared, and although each can be applied in some environments of interest, numerous environments exist in which none are applicable. Therefore, a candidate approach, the Modified Elutriator Method, was also identified that can potentially be applied to some of the environments for which traditional approaches are not helpful. However, although theory supports use of this method, neither the degree with which, nor the circumstances under which, the characteristics of dusts generated by elutriation adequately reproduce those of dusts generated historically (during commercial processing) had been adequately explored. Consequently, to evaluate this approach, elutriated dusts from Grade 3 milled fiber (the predominant type of feedstock used at a South Carolina textile factory) were generated in the laboratory and the characteristics of these dusts were compared to data from published studies of factory dust collected at the South Carolina facility. Elutriated dusts from chrysotile ore were also compared to data from published studies of "factory" dusts collected in Quebec chrysotile mines and mills. Results indicate that despite the substantial variation observed among individual samples within each sample set, the character of elutriated dusts from Grade 3 fiber compare favorably to the character of factory dusts analyzed by Dement et al. and the character of elutriated ore dusts compare favorably to published descriptions of mine dusts.

Given this performance of the Modified Elutriator Method, it was also applied to address an outstanding issue that has been the subject of numerous studies: the disparity in lung cancer mortality per unit of exposure observed, respectively, among chrysotile miners/millers in Quebec and South Carolina textile workers is among the largest and most conspicuous of differences in risk estimates reported across epidemiology studies. Some have postulated that this disparity is due to differences in the sizes of fibers to which each respective cohort was exposed. Consequently, dusts generated by elutriation from three samples each of stockpiled chrysotile ore (representing exposures to miners) and Grade 3 milled fiber (representing exposures to textile workers) were compared.

Results indicate that size distributions of structures in the dusts from each sample differ from one another, which suggests that spatial variation within the mine translates into temporal variation of the ore that is mined and the milled fiber that is produced. Despite such variation within sample types, however, differences between dusts from ore and Grade 3 are statistically distinct with Grade 3 dusts exhibiting significantly longer structures than ore dusts. Grade 3 and ore dust also differ in their morphology and composition. PCM structures in Grade 3 dusts are virtually 100% asbestos and counts of PCM-sized structures are virtually identical,

whether viewed by PCM or TEM (i.e., PCM-equivalent). In stark contrast, about a third of PCM structures in ore dusts are not composed of an asbestos mineral and only about a third of structures counted by PCM are also counted as PCM-equivalent by TEM. These distinctions also mirror the characteristics of the bulk materials themselves. Although Grade 3 looks very much like cotton at a magnification of 8× and as jumbled fibers at 300×, ore samples additionally contain blocky particles that may not be asbestos. Some of these blocky particles may nevertheless be counted as asbestos by PCM (which cannot distinguish among fibers of varying composition). Perhaps most important, when the differences in size distributions and PCM/PCME distinctions in these dusts are combined, the magnitude of the combined difference is sufficient to completely explain the difference in exposure/response observed between the textile worker and miner/miller cohorts. Importantly, however, evidence that such an explanation is valid can only be derived from a meta-analysis (risk assessment) covering a diverse range of epidemiology study environments, which is beyond the scope of the current study.

The above findings suggest that elutriator-generated size distributions mimic those directly determined from factory dusts with sufficient reliability to support comparisons between historical exposures experienced by the various cohorts studied by epidemiologists. In addition, results of a simulation (conducted using the South Carolina factory data) to explore contributions to the variation in size distributions observed between process zones of the South Carolina factory indicate that such variation is driven primarily by the properties of the bulk material (Grade 3) processed at the factory, rather than to differences in the mechanical processes conducted within each zone. This reinforces findings from several geological studies that provide a theoretical basis justifying use of elutriator-generated dusts to reconstruct particle size distributions in historical exposures. Thus, the elutriator may be a valuable tool for reconstructing historical exposures suitable for supporting continued refinements of the risk models being developed to predict asbestos-related cancer risk.

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